Conflicts of Interest

NIH Funding (Past/Pres)
• NIA, NIDDK, NIGMS, NHLBI

CIHR Funding
• RE-ENERGIZE Trial

Mentee Research Grants
• ASPEN, IARS, FAER

Dept of Defense:
• RE-ENERGIZE Trial
• Cardiac Surgery Care

Industry Financial Relationships:
• Consultant/Grant Support: Abbott, Baxter, Cosmed, Fresenius, Musclesound, Nestle, Nutricia, Takeda

Objectives

Describe the international guidelines and clinical evidence regarding the use of indirect calorimetry

Explain the risks of over/underfeeding and the limitation of predictive equations

Discuss current ICU case studies, focusing on the role of Resting Energy Expenditure (REE) measurement in optimizing nutrition therapy
Question:
What is the best method for determining energy needs in the critically ill adult patient?

A3a. We suggest the indirect calorimetry (IC) be used to determine energy requirements, when available and in the absence of variables that affect the accuracy of measurement.

Quality of Evidence: Very Low

ESPEN Guidelines (2018)

Recommendation 15
In critically ill mechanically ventilated patients, REE should be determined by using indirect calorimetry.

Grade of recommendation
B — Strong consensus
(95% Agreement)
Equations that Predict REE Are Inaccurate

- Large discrepancy between measured REE by IC and predictive equations
- Clinical relevant differences in kcal/24h

REE=Resting Energy Expenditure; ESICM=European Society Intensive Care Medicine; R2=correlation coefficient; EPANIC=The Early Parenteral Nutrition Completing Enteral Nutrition in Adult Critically Ill Patients (EPANIC). 1. Central solid line: mean bias; Outer solid lines: limits of agreement between methods (±2SD); Fine lines: confidence intervals of mean bias and limits of agreement.


IC Guided “Isocaloric Feeding” with Trend to Improved Short-term Mortality

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hypocaloric Events</th>
<th>Nutrition Total</th>
<th>Isocaloric Events</th>
<th>Nutrition Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
<th>Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Singer 2015</td>
<td>25</td>
<td>65</td>
<td>21</td>
<td>65</td>
<td>8.4%</td>
<td>1.48 (0.96, 2.24)</td>
<td>2015</td>
</tr>
<tr>
<td>Harmonage 2012</td>
<td>28</td>
<td>57</td>
<td>20</td>
<td>54</td>
<td>6.4%</td>
<td>1.14 (0.93, 1.39)</td>
<td>2012</td>
</tr>
<tr>
<td>Perrie 2016</td>
<td>15</td>
<td>46</td>
<td>12</td>
<td>54</td>
<td>3.7%</td>
<td>0.98 (0.77, 1.28)</td>
<td>2016</td>
</tr>
<tr>
<td>Allegries 2015</td>
<td>21</td>
<td>96</td>
<td>20</td>
<td>93</td>
<td>6.3%</td>
<td>1.26 (0.86, 1.90)</td>
<td>2017</td>
</tr>
<tr>
<td>Total</td>
<td>90</td>
<td>362</td>
<td>129</td>
<td>319</td>
<td>26.5%</td>
<td>1.26 (0.96, 1.67)</td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z=1.84 (P=0.07)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Test for subgroup differences: 2000 kcal/day vs 3000 kcal/day: Z=0.76 (P=0.45)

IC= Isocaloric; H, Random, 95% CI

Dosing of Calories: ESPEN Guidelines on Clinical Nutrition in the ICU

**Recommendation 16**
If indirect calorimetry is used, isocaloric nutrition rather than hypocaloric nutrition can be progressively implemented after the early phase of acute illness.

Grade of recommendation:
0 — Strong consensus (95% Agreement)

**Recommendation 17**
Hypocaloric nutrition (not exceeding 70% of EE) should be administered in the early phase of acute illness.

Grade of recommendation:
B — strong consensus (100% agreement)

**Recommendation 18**
After day 3, caloric delivery can be increased up to 80-100% of measured EE.

Grade of recommendation:
0 — Strong consensus (95% Agreement)

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Appropriate Nutrition Dosing Can Help Decrease Mortality

Calories delivered outside range of 70-100% of REE can increase mortality

Meeting both, targeted calories and high protein, are important for decreasing patient 60-day mortality.

Fewer Nosocomial Infections in Group Fed Closely to Target Measured by IC

Reaching target energy goals (EN+SPN), guided by IC, resulted in significantly decreased hospital-infection rates

Trial Design

Kaplan-Meier Analysis of Nosocomial Infections

Metabolic Monitoring with Indirect Calorimetry

Acute infection in ventilated patients in the intensive care unit

Association between resting energy expenditure and c-reactive protein

- Sepsis is associated to morbidity and mortality
- Apart from CRP and WBC count, additional diagnostic markers are needed to identify signs of infection
- Significant correlation between measured REE and CRP changes, indicating possible signs of an infection with increases in REE

CRP=C-reactive protein; REE=resting energy expenditure; WBC=white blood cells.
The International Multicentric Study Group for IC (ICALIC) Initiative

Indirect Calorimetry is needed to optimize nutrition care
Use is currently limited by practical setbacks
Initiative was taken to develop new technology
To be accurate, easy-to-use, and affordable cost


The Early Evolution of Indirect Calorimetry

1980s
Early IC devices with Douglas Bag methodology
One of the oldest method for sampling expired gas, considered the gold standard for measuring REE

1990s
Current mainstream metabolic carts
Newer devices that can test on patients on ventilator

Early 2000s
New handheld IC
Portable, but cannot be used on ventilated patients

- Large and unwieldy equipment
- Calibration and correct conditions in the room were required for accurate readings
- Specialized technicians were required to analyze a single gas sample at a time
- Ventilator leaks resulted in inaccurate measurements
- Personal computer use is required to record and analyze results


IC, indirect calorimetry; REE, resting energy expenditure.
Next-generation Indirect Calorimetry

Advances in Indirect Calorimetry technology overcome clinical practice barriers

Q-NRG+ Metabolic Monitor by COSMED is

- **Fast**
  - ~10-15 minutes to run test (including warm-up time)
  - Minimal calibration time

- **Accurate**
  - REE within +/- 3% or 36 kcal/day, whichever is greater
  - Range (0-7200 kcal/day)

- **Intuitive**
  - Real-time, user-friendly dashboard
  - Downloadable data in PDF or spreadsheet file
  - Portable and easily transported between rooms
  - Flexibility to use in intubated and spontaneously breathing patients

Rx Only: For safe and proper use of this medical device, please refer to User’s Manual


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Q-NRG+ As A Way To Address The Problem

Q-NRG+ overcomes current barriers

<table>
<thead>
<tr>
<th>Barriers seen in current IC technology</th>
<th>Q-NRG+</th>
</tr>
</thead>
<tbody>
<tr>
<td>Workflow / ease of use</td>
<td>Takes 45-60 min to set up and run test</td>
</tr>
<tr>
<td></td>
<td>Takes ~10-15 min from start to finish</td>
</tr>
<tr>
<td>Size</td>
<td>Bulky metabolic carts</td>
</tr>
<tr>
<td></td>
<td>Lightweight, portable and easy to transport</td>
</tr>
<tr>
<td>Accuracy tested by Mass-spectrometry</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>Accurate and reliable, tested vs. Mass spectrometry</td>
</tr>
<tr>
<td>Flexibility</td>
<td>ICU use limited for ventilated patients only</td>
</tr>
<tr>
<td></td>
<td>Use in ventilated and spontaneously breathing pts</td>
</tr>
</tbody>
</table>

“Why guess when we can measure” – Dr. Pierre Singer, ESPEN Guidelines Chair

Rx Only: For safe and proper use of this medical device, please refer to User’s Manual

3. Oshima T et al., The clinical evaluation of the new indirect calorimeter developed by the ICALIC project, Clinical Nutrition
Timing of IC according to the ICALIC Position Paper

IC should be performed when the clinical condition of patient changes, so that the Nutrition Rx can be adapted to meet the demands of the patient’s altered metabolic state.

IC in SCCM/ASPEN & ESPEN COVID-19 Updates

SCCM/ASPEN Nutrition Therapy in the Patient with COVID-19 disease requiring ICU Care
Updated April 1, 2020

Recommendation 4: Nutrition Dose, Advancing to Goal, and Adjustments
...While energy requirements can ideally be determined by indirect calorimetry, the principle of “clustering” of care is particularly important and we recommend instead using weight-based equations to estimate energy requirements as a practical matter for the COVID-19 patients...

ESPEN expert statements and practical guidance for nutritional management of individuals with SARS-CoV-2 infection
March 24, 2020

2.2. Statement 2
Energy needs can be assessed using indirect calorimetry if safely available with ensured sterility of the measurement system, or as alternatives by prediction equations or weight-based formulae such as:
1) 27 kcal per kg body weight and day; total energy expenditure for polymorbid patients aged >65 years (recommendation 4.2 in ref. [7])
2) 30 kcal per kg body weight and day; total energy expenditure for severely underweight polymorbid patients (recommendation 4.3. in ref. [7])*
3) 30 kcal per kg body weight and day; guiding value for energy intake in older persons, this value should be individually adjusted with regard to nutritional status, physical activity level, disease status and tolerance (recommendation 1 in ref. [8])

In regards to IC, focus is on limiting physical exposure

Longitudinal Evaluation of Energy Expenditure and Metabolic Pathophysiology of COVID-19
LEEP-COVID

Funded in part by investigator initiated research grants from Baxter Healthcare Corporation
Indirect Calorimetry in COVID-19?

LEEP-COVID Study

LEEP-COVID is an ongoing trial. Results shown are preliminary and should not be considered definitive.

Currently, no longitudinal data exist describing EE & metabolism of COVID-19 infection.

Data urgently needed to assist care & recovery of COVID-19 patients worldwide.

LEEP-COVID Study

Aim: Evaluate **longitudinal EE & metabolic pathophysiology in COVID-19** to understand, guide & optimize nutrition/metabolic care

Will provide objective data to guide physical recovery interventions - i.e. nutrition & physical therapy to ensure functional recovery in COVID-19

* Accepted for publication in Critical Care
LEEP-COVID Study Measures

- Longitudinal Measures from ICU Admit - Hospital Discharge
- Every other day in ICU/3 x week on Floor

01 New Q-NRG+ Indirect Calorimetry device
Provides non-invasive cardiac output (via Fick equation)

02 New Muscle-Specific Ultrasound
Measures muscle mass, quality & glycogen content

03 Advanced Bioimpedance Analysis (BIA) Device
Measures body composition via bioimpedance analysis

04 Bedside Cardiac Echocardiography/CV Assessment

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Case Study

This is a mid-50’s LTAC patient COVID (+) (60 kg) early in care (Day 2)

- Spontaneously breathing on vent (not paralyzed)
- 15 kcal/kg is determined by indirect calorimetry
- On Trophic Tube Feeds

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Case Study

This is our COVID (+) patient early in care (Day 4)

- Being fed 1440 kcal/d - based on 18 kcal/kg
- Proned and Paralyzed when test was done on PEEP of 12

What About Chronic and Recovery Phase? Beyond Day 5-7...

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Case Study

COVID (+) 49 y/o patient
(ICU Day 12)

- Being underfed 1440 kcal/d - based on 20-25 kg/kg
- 35 kg/kg/d by IC
- We changed feeding to 2400 kcal/d as patient weaned on vent on pressure support

COVID (+) 49 y/o patient
(ICU Day 15)

- Febrile at time of cart (> 70% of day)
- 44 kcal/kg via IC
- Changed feeding to 2400 kcal/d w/ improved RQ & increased REE as patient weaned on vent on pressure support
Case Study

COVID (+) 49 y/o patient (ICU Day 18)

(Now Afebrile—previous IC measures patient febrile much of day)

- 28 kcal/kg measured by IC
- We changed feeding to 2100 kcal/d to account for febrile & non-febrile periods as patient weaned on vent on pressure support

* Accepted for publication in Critical Care

Case Study

COVID (+) 49 y/o patient (ICU Day 23)

- Being fed < 50% of goal x 7 days
- RQ showing underfeeding and continued protein breakdown
- 34 kcal/kg measured by IC
- Feeding needs continue to be 156% of predicted and EN+SPN being considered

* Accepted for publication in Critical Care
## LEEP-COVID Study

### Baseline Characteristics (n=22)

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong> (median, IQR)</td>
<td>58 (31-88)</td>
</tr>
<tr>
<td><strong>Male sex - n (%)</strong></td>
<td>13 (59)</td>
</tr>
<tr>
<td><strong>Race - n (%)</strong></td>
<td></td>
</tr>
<tr>
<td>• African-American/Black</td>
<td>12 (54)</td>
</tr>
<tr>
<td>• Caucasian/White</td>
<td>7 (32)</td>
</tr>
<tr>
<td>• Hispanic</td>
<td>3 (14)</td>
</tr>
<tr>
<td><strong>BMI (median, IQR)</strong></td>
<td>30.7 (17.4-48.1)</td>
</tr>
<tr>
<td><strong>BMI &gt;30 (%)</strong></td>
<td>12 (55)</td>
</tr>
</tbody>
</table>

*Accepted for publication in Critical Care*
Prolonged Hypermetabolism in COVID-19

Indirect Calorimetry / Nutrition Data:

<table>
<thead>
<tr>
<th></th>
<th>D0-7</th>
<th>D7-14</th>
<th>D14-21</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measured REE absolute kCal/day (all patients) (median, IQR)</td>
<td>1568 (1175-2215)</td>
<td>1830 (1465-2467)</td>
<td>2789 (1776-3262)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Measured REE kCal/kg Actual BW (BMI&lt;30) (median, IQR)</td>
<td>19.2 (16.9-20.7)</td>
<td>26 (24.5-35.5)</td>
<td>29 (23-34.5)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Measured REE kCal/kg Actual BW (BMI &gt;30) (median, IQR)</td>
<td>17.5 (12-19.25)</td>
<td>21 (20-23.5)</td>
<td>31.5 (24.8-36)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Measured REE kCal/kg Adjusted BW (BMI &gt;30) (median, IQR)</td>
<td>20 (17-22.5)</td>
<td>26.3 (24-29)</td>
<td>32.5 (28.8-35.8)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Measured REE kCal/kg Actual BW (all patients) (median, IQR)</td>
<td>19 (13.7-28.5)</td>
<td>26 (22-42)</td>
<td>30.4 (27-35.8)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Actual kcal administered - kCal/kg (median, IQR)</td>
<td>9.4 (0.6-14.5)</td>
<td>13.5 (11-24)</td>
<td>26.5 (13.8-29.5)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>% energy needs actually delivered as determined by measured REE (IBW) (median, IQR)</td>
<td>49.4 (27-58.8)</td>
<td>51.9 (41.5-88.5)</td>
<td>84.1 (83-98.1)</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>

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Respiratory Exchange Ratio (RER ~RQ)

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Prolonged Hypermetabolism in COVID-19

mREE (all pts, Actual BW)

Non-Obese, BMI<30

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Prolonged Hypermetabolism in COVID-19

*Accepted for publication in Critical Care*
Caloric Need Vs Predicted in COVID-19

* Accepted for publication in Critical Care

Prolonged Hypermetabolism in COVID-19

* Accepted for publication in Critical Care
LEEP-COVID Study

<table>
<thead>
<tr>
<th>Clinical Data</th>
<th>D0-7</th>
<th>D7-14</th>
<th>D14-21</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Use of prone positioning (%) (mean, sd)</td>
<td>12.3</td>
<td>7</td>
<td>12.2</td>
<td>0.17</td>
</tr>
<tr>
<td></td>
<td>(8.6)</td>
<td>(2.4)</td>
<td>(4.3)</td>
<td></td>
</tr>
<tr>
<td>Use of paralysis with neuromuscular blocker (%)</td>
<td>14.8</td>
<td>9.7</td>
<td>12.3</td>
<td>0.2</td>
</tr>
<tr>
<td>(mean, sd)</td>
<td>(8)</td>
<td>(1.7)</td>
<td>(3.4)</td>
<td></td>
</tr>
<tr>
<td>SOFA score (mean, sd)</td>
<td>9</td>
<td>9</td>
<td>9.5</td>
<td>0.5</td>
</tr>
<tr>
<td></td>
<td>(3.6)</td>
<td>(3.2)</td>
<td>(3.6)</td>
<td></td>
</tr>
</tbody>
</table>

* Accepted for publication in Critical Care

Use of Prone Positioning and Paralysis in LEEP-COVID

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Severity of Organ Failure (SOFA) Score in LEEP-COVID

![SOFA score graph](image)

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Indirect Calorimetry Data in COVID-19
NCT:04350073

**Initial LEEP-COVID Data**

- **In first 3-7 days**
  COVID-19 patients are NormoMETABOLIC
  (80-100% of predicted/17-20 kcal/kg/d)

- **After day 7**
  COVID-19 patients are HYPERMETABOLIC - 120-200% of equation predicted even paralyzed... (25->35+ kcal/kg/d)

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Indirect Calorimetry Data in COVID-19
NCT:04350073

Initial LEEP-COVID Data

First ICU Week
~20 kcal/kg (Actual BW for BMI < 30 and Adjusted BW for Obese BMI 30-50) are close to mREE

Acute Phase (First 1-5 days?)
Per ESPEN Guidelines would feed 70% of ~20 kcal to prevent overfeeding in non-malnourished pts

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Indirect Calorimetry Data in COVID-19
NCT:04350073

Initial LEEP-COVID Data

After day 7
Considerable variability from day to day exists

Key Factors To Consider in Setting Goals
- **Age:** (Over 70= ↓ kcal/kg/d)
- **Obesity:** (30-32 kcal/kg/d IBW: post-1st ICU wk)
- **Fever:** Significant ↑ kcals (500-1000 kcal/d)

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Hypermetabolism does not appear related to severity of organ failure

Hypermetabolism may only have minor relationship (if any) to paralysis and sedation (such as for proning)

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The effect of cisatracurium infusion on the energy expenditure of critically ill patients

Nutrition Delivery Targets in COVID-19 from LEEP-COVID Data

Adapted from Wischmeyer PE. Crit Care Clin 34:107-125. 2018

- Acute phase (Day 0-7 post-ICU admit)
- Chronic phase (2nd-3rd ICU week)
- Recovery Phase (Post-ICU Discharge)

Kcal/kg/day

Protein (g/kg/d)

- ICU Intubations
- Activity/Rehab Increases

"COVID-19 Patient Proposed Kcal Delivery"
"Traditional ICU Patient Proposed Kcal Delivery"

Personalized Nutrition Rx Using Indirect Calorimetry

01 Perform IC when a nutrition care plan is indicated

02 Use Measured Resting Energy Expenditure to define your caloric target, then define/determine protein target

03 Choose artificial nutrition type (e.g. EN, PN, SPN)

04 Provide optimal nutrition to patients according to target

05 When metabolic needs change, repeat IC and adjust treatment plan/nutrition Rx
Indirect Calorimetry in Nutrition Therapy, Position Paper by ICALIC Study Group

IC should be performed when the clinical condition of patient changes, so that the Nutrition Rx can be adapted to meet the demands of the patient’s altered metabolic state.

Clinical recommendations and integration of Indirect Calorimetry

Indirect Calorimetry (IC) provides individualized energy targets for patients as recommended by international guidelines1,2

Optimal nutrition that meets nutrition targets can significantly decrease patient mortality3

IC should be integrated into the patient’s nutrition assessment/plan4

We hypothesize:

- COVID-19 will lead to significant, EE/metabolic changes, systemic mitochondrial dysfunction, significant muscle wasting and loss of function throughout the course of illness and during recovery.

- Metabolic needs will initially decrease in acute illness and subsequently increase as patients transition from the acute phase of COVID illness to recovery phases. This data will guide nutrition and metabolic clinical care in all phases of COVID-19 care where, for example, over-and under-feeding may pose risk to patient outcome.

- Loss of muscle mass and physical function occurring in COVID-19 will significantly affect nutritional/rehabilitative/recovery of function/qol needs and requires addressing to personalize care to optimize clinical and functional recovery efforts in older COVID-19 patients.

ClinicalTrials.gov Identifier: NCT04350073

Prospective, observational cohort study of 120 patients

Study Questions:
We propose to evaluate longitudinal metabolic and cardiac pathophysiology in patients with COVID-19 to understand, guide and optimize our metabolic clinical care during acute hospitalization. Further, this data will be essential in providing objective data to guide physical recovery interventions including nutrition delivery and physical therapy to ensure functional recovery of COVID-19 patients.

Q-NRG+ Metabolic Monitor Indications and Instructions for Use

The Q-NRG+ portable Metabolic Monitors are indicated for the measurement of Resting Energy Expenditure (REE) for spontaneously breathing and ventilated patients, within the following populations:

- Spontaneously breathing subjects >15 kg (33 lb) when using a canopy
- Spontaneously breathing subjects age >6 yrs and > 10 kg (22 lb) when using a face mask
- Ventilated subjects age > 10 yrs and > 10 kg (22 lb)

The Q-NRG+ Portable Metabolic Monitors are intended to be used in professional healthcare facilities only.

Precautions/Contraindications: Carefully re-check ventilator functionality after connection of the ports. Make sure that the patients cuff pressure is high enough to avoid air leakage. Manipulation of the ventilator circuit may cause leaks that may lower alveolar ventilation.

Indications for Use: The Q-NRG+ Portable Metabolic Monitors are indicated for the measurement of REE for spontaneously breathing and ventilated patients, with some limitations in accordance with labeling, within the following population: spontaneously breathing subjects > 15 kg (33 lb), when tested with the canopy dilution technique, ventilated subjects > age 10 and 10 kg (22 lb), and spontaneously breathing subjects > age 6 and 10 kg (22 lb), when tested with face mask. The Q-NRG+ Portable Metabolic Monitors are intended to be used in professional healthcare facilities only. This device is not suitable for operating in presence of flammable anesthetic gases or gases other than O2, CO2, N2 and water vapor. The device is to be used by physicians or by trained personnel under the responsibility of a physician. The device is not intended as a continuous monitoring device for surveillance of vital physiological processes.

Warnings: This devices measures clinical parameters used to aid diagnosis and it is intended only as an adjunct device in patient assessment. In case of disturbing conditions, the shutdown is allowed because the safety of the device towards patients and operators is not affected, since the final evaluation is performed on the outcome data measured during a complete test. No modification of this device is allowed.

Rx Only. For safe and proper use of this device please refer to the User’s Manual.