



***How Should Glucose Meters
Be Evaluated
For Critical Care***

IFCC Working Group GMECC

Terms of reference 1 and 2

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IFCC WORKING GROUP WG-GMECC HOW SHOULD GLUCOSE METERS BE EVALUATED IN CRITICAL CARE

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EXECUTIVE SUMMARY

Blood glucose meters (BGM) are widely used for monitoring glycemic status in a broad spectrum of patients. However, their use may be associated with risks, especially with critically ill and more fragile or complex patients who may be in a dynamic state and have conditions predisposing them to errors in glucose measurements, especially with strip based meters and capillary samples, and possibly resulting in hypoglycemia and death. While there have been recommendations that BGM not be used with these patients, there is also the recognition of the value and convenience BGM offer, including wider access to testing, shorter turn-around-times, better use of available resources, and possibly lower total costs.

The Food and Drug Administration (FDA) has highlighted concerns about the conditions BGM should meet and the studies needed to assure their performance, first in a 2014 draft guidance and then in a 2016 final guidance, “Blood Glucose Test Monitoring Systems for Prescription Point-of-Care Use”, addressing use of BGM in professional healthcare settings (PHS) on “patients in various states of health and receiving intensive medical intervention and therapies”. This guidance and other professional concerns and documents prompted the IFCC, through its POCT Task Force (POCT TF), to convene a Work Group (WG) to address the concerns and options that the healthcare community should be aware of when considering or using BGM.

The IFCC POCT TF charged the WG with the following:

1. Evaluate the clinical practice of using blood glucose meters for critically ill patients.
2. Determine the requirements a glucose meter needs to fulfill in order to be used for critically ill patients.
3. Propose the internal and external quality control systems that should be present.
4. Evaluate which, if any, of the present instruments in the market fulfill these criteria.
5. Provide recommendations for training and competency of users in critical care areas.
6. Ensure recommendations align with other stakeholders.

This document addresses Terms 1 and 2 of that charge and subsequent documents will address the other charges. While taking the time to build the international and stakeholder input and consensus for this document, certain fundamental principles for best practices guided the WG. These include the necessity for BGM users in any site to be aware of limiting factors associated with BGM in PHS, the need for evaluation and oversight of BGM use to be practical and respect resource issues, but

also for there to be a single high international standard recognizing that any patient in any location deserves the same assurance of quality and reliability in BGM results. To achieve these principles the clinical laboratory and manufacturers need to be key partners in the process and there must be an ongoing effective collaborative quality program at each site.

The document sections cover the following:

Term 1 addresses broadly the factors that can cause BGM results to vary, including clinical conditions, method technology, specimen types, and potential interferences, including medications. Patients with certain physiologic conditions may pose a higher risk of unreliable BGM results and may also have more dynamic and unpredictable states that can affect BGM reliability. It is important to be aware of the known clinical circumstances that contribute to errors when using BGM in PHS. Given the effect that altered perfusion and plasma constituents can have on capillary samples, the WG currently does not support their use with BGM in this group of patients. It is recognized that future developments may change this position.

Term 2 includes more detail on the factors that affect BGM performance in critically ill and PHS patients. It is purposely divided into sections that provide both a basic foundation and specific guidance for readers so that this document can serve as a resource for a broad spectrum of stakeholders in multiple settings. Some of the information may be generally applicable to any point-of-care testing, but the overall focus is on BGM in critically ill and PHS patients so that stakeholders can make the best decisions and provide the best oversight of BGM testing.

Specifically addressed are:

- A. An effective evaluation and selection process for BGM
- B. Comparison of available meters/methodologies, larger analyzers/methodologies, and accepted reference methods
- C. Clinical and technical factors that affect meter performance
- D. Ideal performance characteristics of glucose methods for use in critical care sites
- E. Validation or verification, concepts and details of studies required for BGM

The final current recommendation of the WG is that BGM for critically ill and PHS patients should not currently be used with capillary samples, and that all users should be aware of the variables associated with BGM and the performance assessments that should be done when using BGM. Options for glucose testing in critically ill and PHS patients include alternative glucose methodologies and devices, or arterial or venous samples with meters approved for those samples in critically ill or PHS patients.

INTRODUCTION

Developed in the 1950's to 1970's, blood glucose meters (BGM) were widely adopted for patient self-monitoring of blood glucose (SMBG), doctors' office, emergency department, and hospital in-patient glucose monitoring by the 1980's, thus allowing rapid patient assessment and treatment for glycemic control. In the United States, when the Clinical Laboratory Improvement Amendments (CLIA) regulations were introduced in the early 1990's, these devices were generally classified as waived category and point-of-care testing (POCT), intended for lay user or healthcare professional monitoring of glycemic control in known diabetic patients. Waived laboratory tests were officially defined to be so simple that the risk of errors was slight and the effect of an error was assumed to be minimal. Manufacturers were not required to demonstrate glucose meter performance characteristics or effectiveness in critically ill patient populations or professional healthcare settings (PHS). As glucose meter use broadened, there was more appreciation of their limitations and potential for errors in all patient groups, but most seriously in more complex, dynamic and fragile critically ill patients where the risks of hypoglycemia and death were recognized (1).

Acutely ill patients can exhibit stress hyperglycemia, independent of whether they have pre-existing diabetes. While stress-induced hyperglycemia may be a protective response (2), it has also been associated with adverse outcomes.

Three sentinel studies from Van den Berghe et al reported improved outcomes in surgical, medical and pediatric critical care patient groups in whom blood glucose levels were maintained at normal fasting levels ("tight blood glucose control") by titration of intravenous insulin ("intensive insulin therapy")(3,4,5,6). Because of those studies, tight glycemic control protocols covering high and low target ranges for glucose were widely adopted. However, subsequent studies did not confirm the benefits of those protocols and even showed higher patient mortality. These later studies also found more frequent hypoglycemic events when blood glucose levels were strictly controlled (7,8,9).

There are a number of possible explanations for these different findings, one of which was the difference in glucose testing methods. While the original Van den Berghe et al studies used precise blood glucose analyzers located in the ICU, subsequent studies have frequently used various point-of-care (POC) blood glucose meters (BGM) (10). In tight blood glucose control, BGM are not only used for monitoring blood glucose levels, but also for titrating the insulin infusion rates in critically ill patients. There are also numerous pre-analytical (e.g. anemia and poor peripheral perfusion) and

analytical (e.g. glucose methodology) conditions potentially affecting the accuracy and variability of BGM, especially in critical care patients and PHS. While many studies assessing the performance of BGM in acutely ill patients have been published, they may vary by including different patient populations and sizes with different clinical issues, along with different care sites, sample types, generations of glucose meters, pre-analytic factors, combinations of meters and central laboratory analyzers, and insulin protocols. However, most studies have shown concerns and shortcomings with strip-based BGM (11). There have been recommendations that BGM not be used with critically ill patients, especially with capillary samples (12). However, there is recognition of the value and convenience of BGM in acute care settings, including access to testing, available resources, turnaround times, and costs.

The FDA has organized several meetings addressing these concerns, and has modified its recommended product labeling for manufacturers to indicate whether their BGM have been evaluated for use in critically ill patients or in PHS and what are the “intended use” patient populations that can be tested with BGM. In the US that meant that for many uses what was considered a waived test could default to “high complexity” testing, requiring detailed manufacturer or user validation studies. A few POCT non strip-based devices had been previously FDA cleared for glucose testing in a broader range of patients, but extensive validation studies in critically ill or PHS patients for those devices may not have been fully performed. However, the FDA emphasis on BGM performance has been on strip-based systems.

The FDA released its “Draft Guidance” in January 2014 proposing more rigorous validation recommendations for manufacturers applying for clearance of new meters to be used in critical care settings. That draft guidance was followed in October 2016 by a final guidance, “Blood Glucose Monitoring Test Systems for Prescription Point-of-Care Use” (13). The final guidance modifies some of the emphasis and language of the 2014 draft guidance, especially by changing from a focus on “critically ill” patients to BGM testing in “professional healthcare settings” on “patients in various states of health and receiving intensive medical intervention and therapy.” However, both documents emphasize the importance of recognizing that patients in PHS can be “acutely ill and medically fragile and are more likely to present physiologic and pathologic factors that could interfere with glucose measurements” using BGM. The FDA guidance document describes in detail the accurate definition of intended use patient populations, setting performance parameters that should be met, and documenting the extensive data that is recommended to support using BGM in these complex settings while still allowing them to be classified as waived devices. The 2016 guidance also stresses reducing the risk of blood-borne pathogen transmission and the use of software and connectivity for improving the performance and safety of BGM.

In January 2013 the Clinical and Laboratory Standards Institute (CLSI) released an approved guideline, POCT12-A3, "Point-of-Care Glucose Testing in Acute and Chronic Care Facilities", outlining the studies that users should conduct to verify that glucose meters can perform safely "at acute and chronic care facilities where laboratory support is available" when used for critically ill patients in their specific care settings (14). The FDA guideline is directed at manufacturers, while POCT 12-A3 focuses on users in specific settings. Both documents address desired performance and safety of BGM in PHS.

Other professional bodies have expressed similar concerns about BGM in critical care settings (15). In 2013, the IFCC formed a work group (WG) under its POCT Task Force to address the evaluation of BGM in critical care settings. That WG is comprised of broad-based and internationally involved and recognized members with extensive research and practical experience in blood glucose monitoring and the clinical care of acutely ill patients in PHS. This is the first in a series of documents that the WG will present addressing various topics associated with BGM used for critically ill patients or in PHS. It has taken several years to develop a document as the environment and professional organization consensus building have evolved. The WG has also assiduously worked toward consensus among its large and international membership, including representatives from industry. The WG also elected to include sections devoted to technical and clinical details of BGM, as a foundation for many of its recommendations and as a resource and orientation for stakeholders. While some of the driving forces for review of BGM performance arose in the US, the concerns about BGM performance have been international. The WG has steadfastly adhered to the principles of best practices for any site in the world and best care for any patient population. Ideally, these documents should be collaborative efforts with all stakeholders (e.g. clinical, laboratory-based, manufacturers, and regulatory) involved with BGM and in PHS. The WG members would like this to be an ongoing process of communication and improvement in the acute care and safety of patients who are monitored for glycemic control outside of patient self-monitoring.

In drafting this document, the WG holds the following to be fundamental to any recommendations about using BGM for acutely ill patients and in PHS

1. All users worldwide must appreciate the serious patient safety concerns and full potential for error or variability with BGM when used for unstable and acutely ill patients, especially with capillary samples. This is true for clinical and laboratory users, especially if they have not experienced clinical situations where errors were obvious. Part of the WG's function is to promote international awareness of the potential for error when using BGM in many acute care situations.

2. It is important for users to recognize and define the group of unstable or acutely ill patients who they will test and who may be at higher risk for errors associated with BGM. These users must include the personnel who actually perform the testing, since many operators may not have been fully trained in the limitations or risks associated with BGM. See Term 1 below.
3. IFCC recommendations should be widely applicable and practical.
4. Site and resource testing variables and limitations should be appreciated.
5. However, there should be a single high standard of BGM testing performance and reliability across the world.
6. Different processes or partnerships may be used to achieve acceptable accuracy and reliability for BGM in different settings.
7. However, any patient, in any location, deserves the same assurance of accurate and reliable glucose testing results. Healthcare providers should not be required to use cheaper devices if accuracy and reliability are not ensured and patient safety is compromised.
8. The clinical laboratory should be an essential partner in the evaluation, selection, and oversight of any BGM used in PHS. Laboratory professionals should be viewed as resources for effective glucose testing and monitoring and should actively collaborate with clinical sites to achieve safe and effective testing. (Refer to ISO 22870, Point-of-care testing (POCT)-Requirements for quality and competence (16), and ISO 15189, Medical laboratories-Requirements for quality and competence (17).)
9. Manufacturers are key partners in the development and ongoing performance of effective BGM. They should ensure through formally documented and reviewed validation studies that their BGM can perform reliably in PHS.
10. There must be an ongoing quality program that can assure effective BGM use and detection of any evolving performance issues. This process should involve collaboration with all BGM stakeholders and be actively supported by the clinical laboratory and POCT coordinators or managers. More details about quality management of BGM will be included in an upcoming WG document (Term 3).

The IFCC WG was charged to address the following Terms of Reference:

1. Evaluate the clinical practice of using blood glucose meters for critically ill patients.
2. Determine the requirements a glucose meter needs to fulfill in order to be used for critically ill patients.

3. Propose the internal and external quality control systems that should be present.
4. Evaluate which, if any, of the present instruments in the market fulfill these criteria.
5. Provide recommendations for training and competency of users in critical care areas.
6. Ensure recommendations align with other stakeholders.

This document will address Terms 1 and 2. Subsequent documents will address the other Terms.

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TERM 1: EVALUATE THE CLINICAL PRACTICE OF USING BLOOD GLUCOSE METERS FOR CRITICALLY ILL PATIENTS.

The historical context of glucose meters and the evolution of their use in critical care or PHS have been addressed in this document's introduction. However, there are a number of issues that must be considered to determine if using glucose meters is appropriate in PHS and with acutely ill patients.

Glucose meter performance may vary significantly by patient type or condition and there are different risks of errors or inaccuracies based on meter technology, clinical factors, specimen type, medications, or endogenous interferences. A blood glucose meter that is accurate under "normal" circumstances can produce inaccurate results under a variety of altered physiologic conditions. A glucose meter that performs acceptably for routine monitoring of glucose levels in a stable diabetic patient may be entirely inadequate for use in a critically ill patient where the potential for errors is greater and the consequences of errors are more serious. These issues, as noted below, are more fully addressed under Term 2, sections B, C, and D.

The 2014 FDA draft guidance document recommended that each healthcare setting characterize what it considered to be "critically ill" patients and then perform verification/validation studies or set conditions for testing based on that definition. Using a meter that was not validated for use in critically ill patients would be considered unapproved "off label" use in the US. While the FDA and Center for Medicare and Medicaid Services (CMS) in the US did not specifically define "critically ill", they did use wording such as "complex", "fragile" and in "more dynamic states" for these patients.

Standard medical definitions for critical illness exist and generally include aspects of physiologic instability, variable vital signs, and uncertain prognosis or outcome (1). In general, critically ill patients are patients who require vital organ support in order to survive. Treating patients with critical life-threatening conditions requires continuous and intensive monitoring. This also applies to the monitoring of blood glucose levels, to assess metabolic status, potential complications of glycemic status, and the titration of insulin treatment if needed.

The 2016 final FDA guidance changed the language from "critically ill" patients to a more general focus on patients in various states of health in PHS and recommends identifying sub-populations where BGM are susceptible to a number of errors. That concept has been the original focus of this

IFCC document. It has also been supported in CLSI POCT 17, "Use of Glucose Meters for Critically Ill Patients", as outlined below (2).

For glucose meters there are known clinical situations that interfere with meter performance. Many of these are common in critically ill patients, but they may also occur in other conditions. Rather than just use a clinical definition of critically ill, it is more relevant to consider the clinical circumstances known to cause errors BGM use. Patients at risk for these errors may not only be in intensive care units and may not only be acutely ill, since conditions affecting BGM performance may be present in chronically ill patients and outpatients.

First, capillary or finger stick samples should not be used for BGM in patients with altered perfusion or conditions significantly affecting the normal ratios of plasma constituents. Poor peripheral perfusion or other factors in addition to physiologic changes may cause glucose concentrations in capillary samples to vary significantly from venous or arterial blood. These conditions may be associated with peripheral vascular disease, hypotension or shock, dehydration, hypothermia, hyperglycemic and hyper-osmolar states, edema, and vasopressor treatment.

Besides altered peripheral perfusion, the following categories of clinical features associated with BGM inaccuracy must be considered:

- Very low or high hematocrits that either interfere with strip blood diffusion or change blood water content and glucose measurements
- Hypoxia and acid base disturbances interfering with certain glucose methodologies
- Drugs or other substances such as acetaminophen, triglycerides, uric acid levels, vitamin C, and icodextrin, that, when elevated, can interfere with specific meter and strip technology.
- Altered protein or lipid levels that can also affect plasma water and strip performance
- Sedation or abnormal mental status that may mask clinical signs of hypoglycemia and make it difficult to correlate meter results with clinical presentation

Not all patients will show predictable and clinically significant deviations in glucose readings with the above conditions. However, unacceptable rates of errors have been consistently demonstrated in studies with patients having these changes, leading to a significant risk of inaccurately diagnosing hypo or hyperglycemia.

Finally, critically ill patients are usually in an unstable and dynamic state, so that conditions affecting BGM performance can change rapidly and unpredictably. Users must be aware that it may not be possible to use glucose meters in all categories of patients, and that a meter that performs well in some types of clinical situations may not be acceptable in critically ill patients or PHS where any patient may be in a dynamic state.

Currently, the FDA in the US has not cleared any BGM for use with capillary samples in critically ill patients. One meter has been cleared for arterial and venous samples in this patient population (3). For all the reasons cited above and in other sections of this document, the IFCC GMECC WG does not now support the use of capillary samples with BGM for monitoring critically ill patients or in those conditions where performance can be adversely affected.

There are published and on-going studies to address these concerns (4) and there is recognition that some of the concerns about capillary specimens may be due to physiologic changes while others may represent analytic issues. Insulin dosing protocols and practices may also contribute to risks or errors associated with glycemic control (5), so not all adverse glycemic control events are caused by errors with BGM. Vendors are actively addressing these concerns and working with the FDA or with clinical partnerships to study corrections or evaluation tools to allow the use of BGM with capillary samples and in all clinical settings. At this document's publication the FDA is considering new data to support the use of BGM with capillary samples in critically ill and PHS patients. Recommendations regarding the use of capillary samples may evolve pending more studies and deliberation by professional bodies.

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TERM 2:

DETERMINE THE REQUIREMENTS A GLUCOSE METER NEEDS TO FULFILL IN ORDER TO BE USED FOR CRITICALLY ILL PATIENTS.

The Work Group has divided this Term into the following sections (A-E) to help users systematically consider whether glucose meters should be used in critical care patients or PHS, what factors affect meter performance, and what types of processes should be in place to introduce glucose meters for appropriate clinical use.

A. Creation of an effective evaluation and selection process for glucose meters.

In order to evaluate if a glucose meter will be effective or safe when used for critically ill patients or in PHS, it is essential that users understand the technology and variables associated with meters along with the processes required to assess the performance and risks or benefits of using a meter in that setting. To ensure that all these factors are considered, there should be leadership and representative involvement of stakeholders.

BGM may be the most frequent POC test in most clinical organizations, but management of all POCT activities within an institution is best achieved with formal oversight. While this may not be common practice in all sites, it is advocated and recommended by the National Academy of Clinical Biochemistry (NACB, currently called the American Association of Clinical Chemistry Academy) and other authorities (1,2,3,4,5). This supervision can occur through 1) a medical director with the assistance of dedicated staff or 2) a formal committee of collaborative, multidisciplinary stakeholders. A committee management structure has advantages over a single medical director when debating contentious issues and diffusing emotions over negative decisions or removal of services. The POCT Committee at a minimum should include clinicians, the laboratory director, laboratory representatives or POCT managers or coordinators (see below), and nurses. Membership from purchasing, nutrition support, pharmacy, risk management, information technology, infection control, quality management, administration, and other personnel directly involved with the operations or consequences of near-patient testing can also provide useful input as additions to a POCT oversight committee. These members should encompass the clinical, technical, and operational perspectives necessary for reviewing the indications and patient care needs for new POCT requests, including BGM, as well as the creation and ongoing oversight of a testing program.

Membership of a POCT committee can be flexible with representation that may vary depending on specific organizational needs.

Ideally, this POCT committee provides an educational resource for the indications for use, achievable device performance, potential variables or limitations of use, technical issues, and risks of error when utilizing POCT. The POCT committee provides the necessary quality oversight to ensure reliable POCT results in the various patient populations being tested. An important role of the POCT committee is creation and oversight of the device validation process, development of written policies and procedures, and implementation of the training/competency plan after a device has been selected. This committee should raise the consciousness of staff about POCT errors, set standards of device operation and quality control for end users and improve overall performance, patient safety, and outcomes by its planning and continuous quality oversight.

The clinical laboratory, in any setting, should be an integral and essential member of the POCT committee and play a key role in program development and management. In many settings, laboratory coordination of POCT is managed by designated POCT coordinators or managers, usually laboratory technical personnel who serve as trainers and liaisons between the clinical laboratory and clinical sites that perform POCT. These specialized professionals are invaluable in communicating and overseeing the technical performance of POCT while building alliances and understanding with clinical and administrative peers who deal with the local site practices. In settings where the clinical laboratory is not a key member of POCT selection and implementation, personnel performing those functions must still be capable of providing the expertise and responsibility for ensuring all of the above.

An important responsibility of the POCT committee is the selection of a POCT device that meets specific clinical testing needs and can be utilized throughout an institution, such as a meter for BGM. A single device/model from one manufacturer is easier to manage and more efficient, as only one policy/procedure is required, one checklist is needed for staff training/competency, and device operation is easier to remember for one model versus multiple devices, particularly for floating nurses who may work in different parts of an institution on a regular basis. Ideally, the single selected meter should meet the needs of critically ill and all other patients in an institution.

The general selection process for any POCT device should consider (6):

- Available test menu and turn-around time for results
- Cost-benefit and medical outcomes of POCT versus standard laboratory testing

- Personnel requirements for device operation
- Analytical performance claims that can meet clinical goals and meet international accuracy standards
- Potential for drug, metabolite and other interferences in specific populations of patients
- Frequency of testing and ability of staff to meet requirements for quality control and regulatory compliance
- Ease-of-use and the risk of operational errors or misuse by the operators
- Availability of data-management and connectivity
- Operator and quality control lock-outs and other built-in features to reduce error
- Supply shipping, storage, lot-to-lot variability, expiration dates and other operational challenges
- Complexity of implementing the device and operator training
- Verifying that actual analytical performance can meet clinical expectations by trialing the device using intended operators with actual patient populations

Other considerations for a POCT committee include:

- Establishing a team based process, including the representative stakeholders for evaluation of needs, requests, goals, education, training, compliance, quality management, error detection, process correction, costs, and assigning oversight responsibility and accountability
- Promoting the use of electronic POCT devices with data management capabilities to automate the capture, transfer and permanent recording of quality control and patient test results. Data management provides important safety features, like operator and control “lock outs”, to reduce errors.
- Defining specific patient populations and care sites for performance of each type of POCT
- Specifying qualifications or personnel categories of BGM operators
- Establishing training and competency assessment programs for operators and defining who performs and oversees those programs
- Identifying analytical and clinical goals for intended patient populations
- Assessing the risks or potential errors associated with testing



- Recommending devices that can meet required clinical goals based on device accuracy, usability, reliability, durability, safety, cost, and vendor reputation and support
- Confirming that devices are cleared or validated for specific populations and sites and meet local, national, and professional society guidelines or regulations
- Designing and supervising verification or validation studies that include the anticipated operators, laboratory staff, and patient populations intended during routine use
- Supporting the built in quality, safety, and infection control features for patients and operators
- Developing a program to comply with local, national or international guidelines for test performance and supply procurement, including performance specifications, required features and costs

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B. Comparison of available meters/methodologies, larger analyzers/ methodologies, and accepted reference methods.

It is important that users of glucose meters (or any type of laboratory testing) are aware of the various instruments/devices and methodologies available to them, how those options perform analytically and clinically, and how they relate to reference methods. Understanding specific features of instruments/devices allows appreciation of potential performance benefits or risks. Understanding what constitutes a reference method and how it relates to central laboratory or point-of-care instruments allows users to realistically judge the accuracy and reliability of a glucose meter and the studies needed to confirm performance.

Fully understanding the available options for glucose testing should help in the best selection of a device or instrument that meets clinical needs and provides for the best clinical performance needed.

Description of types of meters and analyzers

Blood glucose meters (BGM) currently in use for patients defined to be critically ill are hand-held devices using test strips based on a biosensor, micro-cuvette system, or cartridges in some cases. The instruments in use usually include a screen that will display the results and error codes when necessary. Laboratory analyzers generally measure glucose very accurately but the sample volume needed, sample types, and turnaround times are limiting factors for critically ill patients. Blood gas analyzers are also accurate, measure a number of analytes needed in critical care, and can accept arterial and anti-coagulated samples. BGM, blood gas analyzers and laboratory analyzers provide intermittent glucose measurements. More frequent glucose measurements can minimize method variables and give a truer picture of glycemic status as noted below. Minimally invasive continuous glucose monitors can measure glucose continuously in interstitial fluid. Invasive continuous glucose measuring systems are placed in the venous blood stream.

Self-monitoring glucose (SMBG) meters (i.e. personal patient blood glucose meters) should not be used in hospitalized patients and may be prohibited for critically ill patients. Although, in general, SMBG may use very small sample volumes and may have shorter measurement times than the hospital glucose meters, SMBGs are not made for the circumstances encountered in critically ill patients. Different regulatory controls may apply to PHS meters, which must be more accurate during more pathologic and dynamic patient conditions such as extremely low and high hematocrits, mixtures of medications, low and high body temperature, variable oxygen tensions,

and high or low blood viscosity, again, situations usually not encountered in people using SMBG for home-use. This document assumes that only BGM cleared for use in PHS are being used in those settings and only addresses issues and performance conditions associated with those meters.

The management, reporting, and assessment of glycemic control lacks standardization. The use of different methods to measure the blood glucose concentration and the lack of harmonization and or traceability to the highest standard leads to contradictory reports regarding the effectiveness and outcome of insulin treatment plans. There is considerable discussion about the accuracy of hospital glucose meters in critical care settings. Studies undertaken with the same POC glucose meters have shown different results. These differences may be related to different populations, settings, and different protocols but they also may be related to the different comparative glucose methods used. With new guidelines emerging, it is important that evaluations are standardized to a true and traceable definitive reference method.

In this section the types of meters are described according to their measurement principle, specificity, variables of influence, proper use, limitations and need for traceability to the highest standard (traceability chain). As stated in the introduction, several glucose methods had been previously cleared by the FDA with a wider “intended use” population than just for the monitoring of patients with diabetes and were suggested, at least in the US, as alternatives to strip-based BGM even if they used similar methodologies and had not been extensively studied in intended use populations, such as critically ill patients (1). The following discussion applies generally to all glucose methodologies but focuses on the comparison of strip-based glucose meters with other testing options. However, for any glucose testing, the issue of sample type is important. Variables associated with capillary, arterial and venous samples are discussed in Sections B, C, and D and can apply to any device.

Enzyme-based methodologies in strip-based BGM

All current strips use enzymes to measure glucose. The enzymes are oxidoreductases.

Principle:

Oxidoreductases oxidize glucose, usually to gluconolactone. All enzymes use coenzymes (or cofactors), and additional enzymes may even be necessary where the overall reaction involves intermediate steps. Electron transfer to an electrode is measured,

Specificity:

The enzyme/co-enzyme complex is responsible for the test strip's sugar specificity, but none of the enzymes is completely specific for glucose.

In general, interfering sugars are not present in the blood of healthy people or people with diabetes. However, in the case of some medications or rare diseases, maltose, xylose, or galactose may be found, leading to false-positive "glucose" readings when a high concentration of enzyme is present or the enzyme is less specific for glucose. Oxidation of interfering substances on the measuring electrode may also affect results.

Imprecision:

The co-efficient of variation (CV%) for BGM is commonly of the order of 5% (5-10%), although the CVs of the newer BGMs are close to 2% in the hands of experienced workers (2).

Central laboratory instruments

Principle:

Central laboratory instruments measuring glucose usually employ hexokinase linked glucose-6-PO₄ dehydrogenase or glucose oxidase based methodology and measure glucose in plasma or serum by spectrophotometry.

Variables of influence:

- Glycolysis in samples can falsely lower glucose values, so rapid testing, removal of cells that can metabolize glucose, and additives or conditions that interfere with glycolysis must be employed to ensure accurate results.
- Anticoagulant preservatives in common usage, such as NaF-oxalate or NaF-EDTA (or the use of ice to immediately cool blood specimens), are not completely effective in inhibiting glycolysis. Addition of citrate, e.g. NaF-EDTA-citrate is the most effective (3).

When to use:

- In routine testing when specimens are rapidly transported and tested quickly or suitable glycolytic inhibitors are used.
- In critically ill patients when patient variables make meter testing unreliable or when meter results are questionable or exceed levels that are reliable with BGM.

Note: Central laboratory instruments are usually used as the comparator methods for glucose meters. It is therefore important to know how each instrument is traceable and aligned to a primary reference method so that accurate assessments of BGM can be made.

Imprecision:

The co-efficient of variation (CV%) for central lab methods is of the order of 1 – 2 %.

Blood gas analyzers

Principle:

Blood gas analyzers are larger than handheld BGM, are usually bench-top models and typically measure blood gases, pH, oxygenated and deoxygenated hemoglobins by co-oximetry and other analytes including glucose. The blood gas instruments aspirate heparinized whole blood that traverses a pathway bringing it into contact with various specific electrodes. Glucose may be measured by a fixed enzyme electrode (usable for a set period) or by using a single use reagent cartridge or a multiple use reagent cassette. Glucose oxidase is the enzyme most commonly used.

Variables of influence:

- Blood gas analyzers usually require a larger sample volume and need a longer analysis time, but are often more accurate than handheld strip based glucose meter devices (4).
- These analyzers are generally considered to be less subject to interferences than glucose test strip based devices, but interferences still exist and need to be considered (see also above).
- Samples are either arterial or venous in origin, so results may differ from capillary BGM samples.

Imprecision:

The co-efficient of variation (CV%) for blood gas analyzers is similar to central lab methods.

Continuous glucose monitors

Continuous glucose monitors are being evaluated in research and comparative critical care studies. One manufacturer has recently secured EU certification for use of a device in the European Union (5) and has also received 510(k) clearance from the FDA for a device to be used in the SICU (6).

Benefits of CGM include:

- Trends in glucose concentration may be more easily anticipated with these monitors since more frequent glucose measurements better reflect true glucose patterns in a patient.
- Statistical analysis of the results of continuous glucose monitoring can provide detailed information on glucose dynamics that could be very useful for research or clinical purposes (7).

Two types of continuous glucose meters are in use:

- minimally invasive (under the skin).
- invasive glucose meters (in a venous space).

Principle:

The minimally invasive glucose meters sample interstitial fluid.

The invasive glucose meters sample the plasma phase of venous whole blood.

Variables of influence:

- The minimally invasive glucose meters suffer from a lag time (up to 20-45 minutes) in reflecting true intravenous blood glucose levels. Patients with rapidly changing physiological conditions may be at risk of suffering from hypoglycemic conditions during these lag times. Continuous monitoring of glucose levels, however, may help in more safely maintaining patients in tight glycaemic control regimens. Subcutaneous (interstitial fluid) measurements must be calibrated against capillary or venous levels and, in some cases such as low peripheral blood flow, even against arterial blood depending on patient condition and procedures performed to treat a patient.
- The invasive glucose monitors use either an in-dwelling catheter like a Swan-Ganz catheter or an infusion needle that is inserted into the blood stream. Due to the frequency of continuous measurements, accuracy or bias are more important factors than imprecision. Frequent measurements minimize the importance of variability between different results, while having an accurate system remains very important. Therefore, calibration of these instruments is of utmost importance.

Limitations:

- In order to compare the continuous glucose monitors with intermittent measurements like laboratory testing, special specimen precautions have to be taken (e.g. turn-around time, low temperature, acidified NaF-tubes, immediate centrifugation) to ensure that laboratory results do not reflect glycolysis or aged specimens.
- A recent study reported that CGM may be very susceptible to interference from acetaminophen and possibly other medications (8, 9). Users should be aware of the possibility of interferences from these and other medications and blood constituents since interferences in CGM may not have been extensively studied.
- Invasive CGM may also suffer from cartridge failures, flow issues, clotting, and “non-reads” (10) and possibly other limitations related to critically ill patients as they are further studied.
- Clinical benefits and accuracy of CGM are still being actively studied in critically ill patients (11).

Blood sample type variables

- For the same conditions, arterial fasting glucose concentrations are slightly higher than capillary blood (0.3 mmol/L, 5.4 mg/dl) that in turn are 0.1-0.3 mmol/L (1.8–5.4 mg/dl) higher than the glucose concentration in venous blood.

- In the fasting state, the glucose concentration in arterial blood can be 0.4-0.6 mmol/L (7.2-10.8 mg/dl) higher than in venous blood.
- In the non-fasting state, glucose concentration in arterial or capillary blood can be roughly 1-4 mmol/L (18-72 mg/dl) higher than in venous blood.
- When reporting glucose values, it is important to be aware of and to state the specimen type and origin e.g. arterial, venous or capillary, plasma or whole blood.

Sample processing techniques in BGM

In addition to these general specimen or methodology-based differences in glucose concentration, it is important to appreciate how the different BGMs process a sample. In general, there are three different categories of specimen processing that differently affect the calculation of a plasma or plasma-like glucose value from a whole blood sample:

1. [Plasma separated by filtration from whole blood.](#)

Principle:

Test strips have absorbent blood application pads with porous layers through which cell free liquid containing glucose diffuses to react with an enzyme reagent.

Variables of influence:

- High hematocrits may influence the diffusion process. Error codes should be present to signal this possibility.
- Most electrochemical strips can show a dependency of current on temperature. Some devices can compensate for this, for instance by measuring temperature and using algorithms to compensate.

2. [Sampling of the water phase of plasma in whole blood.](#)

Principle:

Blood gas analyzers and some glucose meters sample the water phase of plasma in a whole blood specimen resulting in a plasma glucose concentration. These measuring devices filter or exclude cells, proteins and lipids to analyze a water phase. An average protein and lipid content of plasma is then assumed to estimate a plasma-like glucose concentration.

Variables of influence:

- Protein content may vary in critically ill patients. It has been suggested that up to $\pm 4\%$ deviation in the final glucose concentration in an ICU patient sample may occur due to this deviation of the average water phase content of plasma.
- Also, hyperlipidemia may affect the calculated plasma-like value.

3. [Hemolysate from whole blood.](#)

Principle:

In the hemolysate method the glucose content in cells (lower glucose) is mixed with the glucose content in the plasma phase

Variables of influence:

- Hemolysate applications assume that the equilibrium between plasma glucose and glucose inside the erythrocyte is rapid and that glucose is not changing rapidly in the plasma phase of whole blood. Non-fasting patients have a higher glucose in plasma until equilibrium is reached with the inside of the cell. Mixing cell contents with plasma in these cases can therefore result in a lower glucose value than if measured only in the plasma phase.
- Elevated or decreased protein, lipid or hemoglobin concentrations can affect readings, resulting in increased or decreased glucose values.

Primary Reference Method

The authors of this IFCC document accept that Isotope Dilution Gas Chromatography Mass Spectrometry (ID-GCMS) is hierarchically the highest method of quantification available for glucose i.e. the primary reference method. This method can be very accurate (i. e. very small bias) but because of the complexity of the method, precision is usually less than for laboratory analyzers. This method is difficult and not suitable for routine clinical service.

Briefly, during ID-GCMS analysis an isotope labeled glucose is added to whole blood, plasma or serum. The ratio between the signal (m/z) produced by glucose and the signal produced by the isotope labeled glucose times the concentration of the isotope determines the original concentration of glucose in the sample of analysis.

Central laboratory methods are more feasible for high throughput clinical service. They have low imprecision but may still suffer from some bias and interferences. In evaluations of POCT glucose methods, central laboratory methods are usually considered to be the best comparator methods, although in some circumstances blood gas analyzers may be an acceptable comparator method, if properly validated and verified. Comparator methods should be traceable and aligned to ID-GCMS.

Traceability and Comparability of glucose methods

While BGM end users may not be involved with the details of establishing comparability to a reference method, they must be aware of the concept and the need to be informed by the manufacturer of how comparability was traced or established so that accuracy can be ensured.

Not only the central laboratory method, but also the POC method, must be closely aligned to the ID-GCMS method for plasma glucose measurements. This type of method traceability approach is essential in evaluations of POC glucose methods. The manufacturer will usually have demonstrated this as part of the validation of the method and the user's Laboratory / POCT Committee should confirm comparability to the central laboratory method as part of the verification process (see section E on Validation and Verification).

The alignment of a central laboratory method to the ID-GCMS method will usually be established by the manufacturer of the central laboratory analyzer, but laboratories should confirm this with NIST standards or other standards which are well defined and traceable to primary standards (The assigned values for these standards should have a maximum uncertainty of 2%.) Proficiency testing may also cover this need. The maximum allowable deviation for the alignment of the central laboratory method with ID-GCMS or NIST Standard is 4%. If results from POC glucose methods are used in any research publications, information about the traceability and comparability of the methods should be included.

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C. Clinical and technical factors that affect meter performance.

Understanding the known variables affecting glucose meter performance, should help users to select a more appropriate device and create a more effective quality program to minimize errors and unnecessary patient risks. This should ideally guide better training, competency assessment, and monitoring programs to recognize and prevent known sources of error or unacceptable performance. The FDA 2016 guidance document addresses these factors for manufacturers of BGM to study and document affects, but users must also incorporate consideration of these variables in their selection, verification, and quality processes.

Hematocrit, red cell water, and plasma water:

- Many glucose meters report plasma-equivalent glucose values using a fixed conversion factor to account for the normal ranges of water content of plasma and red blood cells, including the normal range of percent red cells in plasma (hematocrit).
- Errors in these assumptions can result in > 10% error for a substantial number of hospitalized patients. Anemia (low hematocrit) is the most important factor, but plasma water content also varies significantly in acutely ill patients due to abnormal plasma protein (1).
- While the “hematocrit” interference is most concerning for glucose meters, whole blood glucose measured by devices other than glucose meters can still be affected by an abnormal hematocrit (2).
- All glucose meters are impacted by an abnormal hematocrit to some extent. Meters that detect and correct for abnormal hematocrits provide more accurate glucose measurement in a hospitalized or critically ill patient population (3, 4), though no meter can completely correct for extreme ranges in hematocrit. The range of acceptable and/or observed hematocrits is an essential consideration in validation or verification studies (see section E).

Limitations of capillary sampling in certain patient populations:

- Patients on vasopressor therapy (5, 6), patients with significant peripheral edema (5), patients in shock or with severe hypotension or dehydration, patients with poor tissue perfusion (7), patients with ketoacidosis (8) and some critically ill patients (9) have been reported to have very inaccurate capillary glucose values. See Term 1.
- Reports citing these limitations have been small observational studies. No specific limitations in blood pressure, medications or other conditions are known that can either identify patients likely to have inaccurate capillary glucose values or identify patients for whom capillary glucose measurement is safe and effective.

- This effect is assumed to represent a physiologic limitation of capillary glucose measurement, wherein poor peripheral perfusion or circulation results in lack of equilibration between capillary and circulating blood glucose concentrations. However, the impact of measurement technology on capillary glucose measurement in these patients has not been studied, so an effect of measurement technology on accuracy of capillary glucose cannot be excluded.

Medication and other interferences:

- Numerous medications have been reported to interfere with various glucose meter technologies. Acetaminophen and ascorbic acid (vitamin C) are two common medications that may interfere with current meter technologies (3, 10). Icodextrin, intravenous immunoglobulin, and other medications containing non-glucose carbohydrates (see below) may be of particular concern for some methods.
- Interference by non-glucose carbohydrates, such as maltose, xylose or galactose, with some glucose dehydrogenase methods has resulted in death and adverse outcomes for both hospitalized patients and outpatients (11,12). Changes in the enzyme-based systems have helped to overcome these interferences, see below.
- Many medication interferences, such as the above, have been reduced or eliminated with newer glucose meter technologies. Evaluation of potential medication interferences, from published literature references and/or in vitro experiments, should be a critical part of method validation or verification (see Section E).
- Analytical interference from hemolysis, icterus (bilirubin), lipemia, uric acid, and other endogenous or biologic interferences should also be considered. Device manufacturers often have information available on the extent of these interferences.
- The 2016 FDA final guidance document gives detailed direction on the types of interferences that should be considered and how they should be evaluated by manufacturers. The studies they describe are also helpful for users and guide evaluation of new potential interferences, such as new medications. The CLSI document, EP7-A2, "Interference Testing in Clinical Chemistry", is also a fundamental guidance for these considerations and studies (13).

Differences observed between whole blood glucose drawn from venous vs. arterial intravascular catheters:

- Studies comparing the reliability of BGM measurements on samples taken from arterial or venous lines have some limitations. These include different meters and central laboratory measurement combinations, different or limited patient populations, small patient populations,

inclusion or knowledge of all significant interfering factors, limited numbers of glucose samples at the extremes of possible values, and different clinical practices.

- Some consider arterial whole blood as a superior sample compared to venous catheter blood, but this is not a uniform finding. Users should be aware of potential differences or biases in BGM when used with samples from different arterial or venous access sites, especially when different patient conditions or populations are considered and different clinical practices for obtaining samples are used (14,15,16,17).
- Users should also include arterial and venous catheter samples in comparison studies when they are verifying the performance of BGM with critically ill or PHS patients who might be monitored for glycemic status in their clinical setting.

Effects of pH, pO₂, and pCO₂:

- pH, pO₂, and pCO₂ are all reported to affect some glucose meter technologies (2,18).
- Some newer whole blood glucose technologies have reduced or eliminated these effects.

User errors are more likely encountered when using capillary samples.

- Failure to clean finger skin, let alcohol or disinfectant dry properly, milking fingers and getting interstitial fluid, or using alternate or unapproved skin sites can affect results.
- Newer glucose meter technologies may have features that reduce or prevent strip under-dosing, such as very small sample volumes required for testing.

User errors not related to sample type:

- Incorrect patient identification, expired, incorrectly stored or incorrectly transported glucose meter strips (especially strips exposed to temperature or humidity extremes), failure to perform quality control or act on out of range quality control results, improper disinfection of devices or strips, strip contamination or decay due to improperly closing strip bottles, improper calibration code or information used for given lot of strips, reporting glucose results in the wrong units (e.g. mg/dL instead of mmol/L), failure to properly flush indwelling catheters or use proper discard blood volume are all user errors that can significantly impact results (19).
- Failure to monitor glucose levels at correct time intervals, act appropriately on a result, or to properly follow an insulin dosing protocol pose risk for glycemic control practices.
- Extremes of temperature and/or humidity during transport or storage of glucose meters or strips can have a relevant negative impact on glucose measurement accuracy (20). Temperature effects have been observed not only during extremes anticipated in transport to hot remote or

underserved healthcare sites (20), but also during routine storage of strips in colder climates such as Canada (21).

- Multiple sources of error associated with BGM are also listed in the 2016 FDA guidance document. CLSI EP-18A, "Risk Management Techniques to Identify and Control Laboratory Error Sources", (22) and ISO 14971, "Medical Devices-Application of risk management to medical devices" (23), are additional guidance documents for error assessment.

Conclusions:

Technical limitations of glucose meters (especially the hematocrit effect) should be considered during selection and validation/verification of glucose meters to be used on critically ill patients. Limitations of capillary sampling (presumed to be mainly physiologic) must be considered in validation/verification studies and in determining the intended clinical use (particularly acceptable sample types in critically ill patient populations) of any glucose measurement system.

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D. Ideal performance characteristics of glucose methods for use in critical care sites.

This section will help users go beyond a general awareness of variables affecting glucose meter performance to considering more specific performance characteristics of prospective or selected meters in different PHS. The 2016 FDA guidance document also addresses many of these issues.

BGM for use in critically ill patients, with the intended use of blood glucose control as well as monitoring, need to meet the following requirements:

Comparability with comparator or central laboratory method

To verify BGM comparability to a central laboratory method, the guidelines of POCT12-A3 and local guidelines for POC blood glucose testing in hospital settings should be used. POCT12-A3 states that under the following conditions glucose meter performance is acceptable for use in hospitals:

- 95% of glucose results are within $\pm 12.5\%$ of the lab method result for glucose values ≥ 5.55 mmol/l (100 mg/dl) and within ± 0.67 mmol/l (12 mg/dl) for glucose values < 5.55 mmol/L (100 mg/dl)

In addition,

- 98% of glucose results should be within $\pm 20\%$ of the lab method result for glucose values ≥ 4.2 mmol/l (75 mg/dl) **and** within ± 0.83 mmol/l (15 mg/dl) for glucose values < 4.2 mmol/l (75 mg/dl).

The laboratory method used for the comparison should have imprecision $\leq 2.9\%$, bias $\leq 2.2\%$, and total error $\leq 6.9\%$ and be traceable to a reference method as addressed in POCT12-A3.

Although no special performance guidelines are applicable to the ICU setting, manufacturers need to validate the comparability of their POC BGM with a comparator method by using sufficient number of samples from critically ill patients (the "intended use population"). BGM users need to verify the manufacturers' claims. If the manufacturers did not do a validation of comparability in the intended use population, this would need to be done by the users, taking into account the critically ill patient population to be tested (pediatric and adults), blood glucose target range, and insulin titration protocol at their testing sites. For further details of validation and verification requirements, see section E.

Imprecision and bias targets

No specific, scientifically supported, imprecision, bias and linearity targets are in place for BGM with intended use in the critically ill patient population. Imprecision should be assessed, as a function of

the chosen target range for blood glucose control. When POC BGM are to be used in the pediatric ICU population, good accuracy and precision in the lower ranges (<4.2 – 5.5 mmol/L, <75-100 mg/dL) are important. If blood glucose levels are to be measured within a narrow target range for glycemic control, good accuracy and precision are required for that range. Bland-Altman (or difference) analysis is used to assess acceptable performance under these conditions, since it does not just look at the relationship between two methods (like a correlation coefficient) but instead demonstrates whether the two methods agree on the quantity or level of analyte measured. Bland-Altman plots also show measuring agreement in different analytical ranges and do not smooth out method relationships, like correlation coefficients do, over a wide range of results.

At minimum, the 95% confidence interval on a Bland-Altman analysis of a POC BGM versus a reference or comparator method should be smaller than the target range of blood glucose control. (1,2). Blood glucose control in the strict target range of the original Leuven studies, 4.4 – 6.1 mmol/L or 80-110 mg/dL, may only be possible with very accurate blood gas analyzers. Less stringent blood glucose control, below 8.3 – 10.0 mmol/L or 150-180 mg/dL, while avoiding hypoglycemia below 3.9 mmol/L or 70 mg/dL may be managed by POC BGM (3). This 95% confidence interval of the POC BGM should be demonstrated by the manufacturer in the hypoglycemic range (< 3.9 mmol/L or <70 mg/dL), normoglycemic range (3.9 – 7.0 mmol/L or 71-126 mg/dL) and the hyperglycemic range (> 7.0 mmol/L or >126 mg/dL).

While increased frequency of blood glucose measurements may to some degree compensate for sub-optimal precision, the frequency of blood glucose measurements should depend on the condition of the patient and the insulin dosing protocol in use in the institution (4,5,6). Good precision is required across the whole of the measurement range, including the extremes of the measuring range.

Imprecision and insulin treatment protocols

The impact of imprecision of a POC BGM on insulin dosing errors is highly influenced by the insulin treatment protocol, as demonstrated in several simulation studies (6). Therefore, insulin treatment protocols should be validated locally before routine implementation in the ICU. This validation should at least document the incidence of hypo- and hyper-glycemia before the protocol implementation and a regular evaluation of these preset markers of glycemic control during and after the implementation (7). Since all guidelines advise against the use of the original tight glycemic control target range (4.4- 6.1 mmol/L or 80-110 mg/dL), two main target ranges are now commonly used: maintaining blood glucose below 10 mmol/L or 180 mg/dL or below 8.3 mmol/L or 150 mg/dL (8). Mild hypoglycemia is being defined as blood glucose levels below 3.9 mmol/L or

70 mg/dL, while blood glucose levels below 2.2 mmol/L or 40 mg/dL are regarded as a severe hypoglycemia.

Modelling studies, using different methodologies, have given some indication on the acceptable measurement error of POC BGM in critically ill patients (4,5,6). For POC BGM, the mean absolute relative deviation (MARD), a measure of statistical dispersion, should definitely be lower than 15% to avoid acutely life-threatening insulin dosing errors and lower than 7% for also avoiding potentially life-threatening insulin dosing errors. Acutely life-threatening errors are erroneous dose calculations that certainly lead to severe hypoglycemia. Potentially life-threatening errors are incorrect insulin dose calculations that may result in hypoglycemia or severe hyperglycemia. Expressed as total analytical error (TAE), in order to avoid acutely life-threatening insulin dosing errors, TAE should not exceed 15.7% and not exceed 10% to avoid potentially life-threatening insulin dosing errors. (Total analytical error combines an assessment of method accuracy or bias with precision or imprecision to judge the analytic performance of a testing method.)

Coefficient of variation (CV) is a measure of glucose meter precision, and should not exceed 10% to avoid hypoglycemia, episodes of hyperglycemia, and blood glucose variability. Ideally, CV should be lower than 5%, which is in line with the FDA and American Diabetes Association (ADA) guidelines. The use of error grids (modified Clarke, Parkes, surveillance error grid) should be discouraged as these were (1) not designed for these purposes and not validated in critically ill patients, (2) do not take into account the varying insulin dosing algorithms and (3) require large number of samples for use (1).

For intensive care physicians it is important to realize that more precision is required when POC BGM are used, not only for monitoring blood glucose levels, but also for deciding on insulin dosing in a blood glucose management protocol. Overestimations of blood glucose levels may lead to overtreatment with insulin and severe hypoglycemia, which may be life threatening. This requirement and potential iatrogenic danger cannot be over emphasized.

Effect of haematocrit, pO₂ and pH

In critically ill patients blood glucose measurements are affected by varying levels of hematocrit (Hct), pO₂ and pH. Different glucose measurement methodologies may be affected to differing extents by these factors. Some meters have additional technology that can correct or compensate for these interfering factors. The manufacturer should report the acceptable working range for these interfering factors. The 2016 FDA guidance recommends that the operating range for hematocrit should at least be 10-65% given the intended use patient population in PHS. A manufacturer may claim a smaller operating range for hematocrit with its meter, but that should be

clearly indicated with the product information. Not only should manufacturers state the operating range for Hct, users should also know the tolerance limits for the POC BGM they are using as demonstrated in verification studies. For pO₂, a recommended minimum operating range of 5.32 – 26.6 kPa (40 –200 mm Hg) was recommended by the FDA in the January 2014 draft guidance to manufacturers developing BGMs for prescription POC use. The 2016 FDA final guidance document is more general, recommending that a broad range of blood oxygen levels be studied, corresponding to levels seen in the intended use patient population. A site’s altitude should also be considered when planning to select or verify a BGM.

Interference from medications and other blood constituents

Meters and/or test strips should ideally be free of interferences from medications, sugars, colloids, lipids and other blood constituents, etc. and/or should have technology to compensate for such interferences. See section C for further details of these interferences. Manufacturers should have carried out interference studies for a range of possible drugs and interferents in their validation studies and provide full information on these studies to users. The FDA, in its October 2016 final guidance to manufacturers developing BGMs for prescription POC use recommends a list of medications and blood constituents which manufacturers should test for potential interferences. However if new or experimental medications are to be used in a particular clinical setting, the user should evaluate these for potential interference with POC BGM. The 2016 FDA guidance provides models for performing those studies. CLSI EP7-A2 is also a guidance document for these studies.

Meter displays, electronic features and connectivity

For use in critically ill patients all BGM should be connected to the laboratory information management system and the hospital information system. This is crucial for the follow-up of possibly erroneous blood glucose measurements and the detection of hypoglycemic episodes in the critically ill patients. The post-analytical data and the quality control data should be jointly reviewed by laboratory representatives, ICU clinicians and IT representatives. To facilitate this auditing, the blood glucose measurements should be stored in a convenient report format. When connectivity is not available, the users should be required to keep good records for traceability to enable audits and to investigate possible problems. The capability to enter patient identification (ID), staff ID and reagent or strip lot numbers, either by barcode or other connectivity, should limit data entry errors. QC and user lockout capability is desirable. Screens should be easy to read and understand and only changeable by qualified personnel. This includes the results, the units for results, and the error codes. User messages, prompts, and error messages or alerts should guide the user in correctly responding and avoiding mistakes. The ideal is to have a fully guided and traceable record of POC blood glucose monitoring.

Minimizing infection risk

The use of POC BGM and strips should be associated with low infection risk and avoid the risk of viral transmission or resistant bacteria, especially in patients with a suppressed immune system. Meters and test strips should thus be designed so that blood does not enter the meter. Meters should also be easily cleanable. Additionally, effective cleaning and disinfection procedures should be provided by the manufacturer and should not introduce measurement errors or affect meter performance. Procedures to minimize infection risk should also cover test strips, strip bottles and carriers for BGM equipment, which can also be sources of nosocomial infection (9, 10). Users and manufacturers should consider ways to reduce these risks. One way of reducing risk is to assign a separate bottle of test strips to each patient with suspected or diagnosed infections. Users should follow national and local procedures regarding cleaning and disinfection. CDC recommends carrying out these procedures after every use if meters are shared. The 2016 FDA final BGM guidance document also emphasizes these issues and stipulates the conditions a manufacturer must cover and document to reduce the risk of blood-borne pathogen transmission. The FDA and CDC have issued other documents and guidance addressing this risk and potential mitigations (11, 12, 13).

Pre-analytical factors affecting quality of results

Users of BGM must appreciate that analytical factors are only one part of the potential for errors and wrong insulin dosage. Pre-analytical errors involve dealing with the way the sample is managed before the actual analysis. These include the drawing of the appropriate sample (e.g. void volume from arterial or venous line), adequate sample volume, avoiding delays in the measurement of blood glucose, correct patient identification, and using properly maintained test strips. Post-analytical errors involve the way the results are linked to the right patient and communicated to the user, inadvertent change of units and wrong treatment decisions or failure to act on results. It is therefore essential that adequate training and on-going quality programs are set up for the users in order to reduce pre-analytical, analytical and post-analytical errors. The 2016 FDA BGM guidance also gives a table of potential pre-analytic, analytic and post-analytic sources of error. These issues will be further addressed by the WG under Term 3.

Blood volume requirements and response time

Required blood volume and response time are much less important in the ICU setting. As the use of capillary blood is not recommended in critically ill patients, the volume of blood currently required by available meters / strips may only be a problem in neonatal and pediatric ICUs. Accuracy is more important than response time. Longer response testing times (endpoint measurement rather than kinetic) may be associated with better accuracy.

Sample type

As previously stated in Term 1, the WG emphasizes that capillary samples from critically ill patients and patients having conditions known to compromise meter performance, should not be used with BGM. Using alternative analysis methods for glucose or using arterial or venous samples in meters cleared for use with critically ill patients is recommended.

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E. Validation or verification, concepts and details of studies required for BGM.

This section should assist readers in understanding the distinction between validation and verification processes and how validation or verification studies should be approached for BGM.

The terms validation and verification are frequently used interchangeably but they actually describe **two very different processes and purposes**. The following explanations are for environments that require a regulated process for test development and implementation such as recommended by the FDA or European Commission (CE), but they also describe a **best practice model that all sites should use**. The IFCC WG for GMECC endorses the adoption of best practices for BGM. Understanding the distinction between validation and verification is extremely important for BGM users, particularly for acute care or critically ill patients, since most current meters were not developed for these clinical situations. The meters may not be able to perform adequately for those patients and may pose significant risk of poor outcomes.

Validation refers to the original “establishment” of a test and is usually done by a manufacturer. However, **if a user changes any conditions of a previously cleared test, such as the technical testing process, specimen type, site of use, or intended use population, that user must perform complete validation studies for these conditions**. Significantly changing a test or creating a new test is considered to be a manufacturing process requiring formal validation studies.

Verification refers to the user “confirming” that a test can perform as claimed by the manufacturer, at the actual site where the test is performed, on the patients who will actually be tested, and by representatives of the actual operators who will be performing the test. **Verification implies that no modifications to the test are made, either in the testing process, the site where testing is performed, or the patients who are tested. If a user changes any previously cleared aspects of the test, then validation studies must be performed**. In the US under the current regulated “test complexity” model, most blood glucose meters are cleared by the FDA and the Centers for Medicare and Medicaid Services (CMS) as “waived” tests. Changing any cleared condition of meter use would mean that a meter would immediately be considered as a “high complexity” test and complete validation studies would be required. Even outside of the US, changing conditions of officially approved meter use would mean that manufacturer tested “intended use” was not being followed and best practices would require that a user should validate meter performance under the new use conditions. In any location, use of glucose meters for critical care patients or professional healthcare settings (PHS) requires the highest standards and practices.

Validation studies, as set by the FDA or CLIA recommend the following studies be performed in environments similar to projected use, on the types of patients who will be tested, and by the types of operators who will be doing testing:

- Accuracy, demonstrating traceability or comparability to an accepted reference or comparator method
- Precision or reproducibility of results
- Analytical sensitivity, including limit of detection or lower limit of quantitation (LOD or LOQ) of glucose by the meter
- Analytical specificity, including possible interferences
- Reportable range of results that can be used, as demonstrated by linearity and accuracy studies
- Reference intervals for the intended patient population (For some analytes, such as glucose, medical decision points or ideal target levels are used instead of a range of "normal" values in a population.)
- Calibration protocols should be established, documented and validated
- Quality control protocols should also be established, documented and validated
- Other characteristics as needed (including known test limitations, such as extreme hematocrits, oxygenation, perfusion, etc. in critical care patients with BGM testing)

The studies should also demonstrate both analytical acceptability and clinical usefulness of a test for the patient populations being tested. A test may be analytically sound but have no real clinical utility. For BGM in critically ill patients or for intensive insulin dosing protocols, clinical utility involves validating the accuracy and safety of using glucose meters in these situations.

Similarly, in Europe, under the IVD Directive (1998, 2011), companies wishing to have their products CE Marked, must provide evidence to validate their performance claims for the product.

Verification studies as required by CMS under the Clinical Laboratory Improvement Amendments (CLIA) regulations in the US include the following studies to demonstrate that a testing site can show performance levels comparable to those established by the manufacturer:

- Accuracy as judged by comparability to an acceptable existing validated method (a central laboratory method is preferable, but if not available, a validated and verified blood gas analyzer may be used)

- Precision or reproducibility
- Reportable range of test results for the particular test system
- Confirmation that reference ranges established by the manufacturer are appropriate for the testing site's patient population. (In some situations a medically desired target range or value will be used)
- Other studies that users should consider to confirm that the method is satisfactory for a particular population or site, e.g. patients with critical illness conditions, patients on various medications, sites with different environmental conditions or types of operators, etc. These conditions should have been previously validated by the manufacturer, but testing sites should include a range of patients and testing conditions in verification studies to ensure that a device can perform acceptably with their patients and in their environments.

There are a number of resources available to guide users in doing proper validation or verification studies. These include the CLSI method evaluation documents, the Association for Clinical Biochemistry and Laboratory Medicine UK (ACB), and other professional resources. The CLSI POCT12-A3 Approved Guideline "Point-of-Care Testing in Acute and Chronic Care Facilities," (cited previously) provides guidance and templates for performing user verification of a manufacturer validated glucose meter at acute and chronic care facilities with laboratory support. The IFCC WG GMECC endorses the principles and examples provided in that Approved Guideline.

POCT12-A3 addresses a number of important issues as outlined here and also addressed in other parts of this document:

- The process of introducing and verifying BGM requires the coordination and cooperation of multiple departments because it involves different operators, specimens, and technologies
- Leadership must be identified to oversee BGM with a defined program of management, selection of devices, quality management, and to meet applicable regulations and accreditation requirements
- Operators must be trained and demonstrate competency
- Patients who will be tested must be defined along with approved operators
- Manufacturer claims must be verified
- Comparisons to central laboratory testing must be performed
- Appropriate use situations must be defined along with the performance of glucose meters in glycemic control protocols

- Limitations of testing must be identified and communicated, including when BGM is not appropriate, when laboratory testing is required, and when discordant results must be investigated
- Standard operating procedures (SOP's), processes, and training must be in place to ensure the above
- Meter performance characteristics must be assessed, including imprecision, trueness, and linearity
- Performance characteristics must be evaluated in patients over the range of potential glucose levels, i.e. hypoglycemia, euglycemia, and hyperglycemia
- CLSI documents are available to guide performance studies
- Ideally, studies should be done with patient samples but commercial materials may be used for reproducibility and linearity studies
- Comparison studies should be performed by operators who are properly trained for meter operation and who understand the factors or variables associated with various specimen types
- Comparison studies must provide for inhibition of glycolysis so that glucose values are truly comparable between specimens and time intervals
- The verification plan must be well planned, documented, and detailed, defining specimen types, fresh versus altered blood, numbers of samples to be tested, and variables that can affect results
- The comparator method, usually the central laboratory analyzer, must have known accuracy and comparability to a reference method, along with documented imprecision, bias, and total error
- Samples must be run in duplicate
- Accuracy and error targets are given in POCT12-A3 and discussed in section D
- Several lots of strips should be tested and provisions for testing new strip lots must be defined
- Detailed suggested comparison protocols are outlined, including the inclusion of essential patient data such as hematocrit, and other possible variables (e.g. pO₂)
- Documentation and data management techniques for evaluation are suggested, along with forms for documenting adverse events and other information
- Comparability protocols require split samples using either material left over from clinical blood specimens or specially taken capillary specimens, in which case ethics and research board or an

institutional review board (IRB) approval may be required, since capillary blood comparisons can require multiple samples and a change in the way a patient may be tested. **The capillary samples can only be used with cleared waived blood glucose meters in patients who are not critically ill or have no factors that affect measurement of glucose in capillary blood, as discussed in Term 1 and prior Term 2 sections. The 2016 FDA final guidance document outlines manufacturer studies that should be done to assess whether a BGM can perform acceptably in all categories of patients in PHS. However, users should verify manufacturer claims, especially in critically ill patients.**

Usual laboratory comparison studies may only involve splitting samples from the same specimen type or containers. Those routine studies generally compare the analytic accuracy of different devices or methods. BGM comparison studies in critically ill patients are complicated by a variety of specimen types and patient conditions that must be covered. They may be further complicated by having several different analyzers or measuring device types used for the same group of patients. In addition to **analytic accuracy**, BGM comparability studies involve **physiologic differences** between patients, specimen types, and the way different measuring devices handle or respond to specimen and patient variables. These issues are discussed in Sections B and C.

Ideal glucose comparison studies are complicated under these circumstances. They require detailed planning and documentation, and must be highly coordinated. They must also account for complex and dynamic patient states and they must be performed by stakeholders who appreciate and can address all these variables. There is clearly a dilemma or challenge in complying with best practices for glucose meter verification in critically ill patients or PHS, covering all the analytic and physiologic issues, and creating a practical and achievable process for all potential users.

While individual institutions or sites may modify or adjust their specific verification plan, the concepts and steps POCT12-A3 suggests should be a model for all sites. However, this IFCC document re-emphasizes key points. **Verification studies should be conducted with the involvement and test performance of actual users, at actual testing sites and including a representative sample of patients having conditions of the intended use population. Clinical conditions known to interfere with accurate testing by the chosen method or device must be excluded from verification studies and, more importantly, from actual patient testing.** However, this premise assumes that users can actually assure that those conditions and patients can be realistically identified and excluded from testing.

For BGM, these exclusion conditions would include extreme ranges of hematocrit, impaired perfusion for capillary testing, known interferences, and any other condition or patient type that the manufacturer notes as a test limitation or that has not been officially validated and cleared for inclusion with BGM by the manufacturer of the meter being considered. There must be alternative options for glucose testing under those conditions. Clinical sites should ensure that users are trained about these testing exclusions and that a quality program monitors the correct use of a meter. **Having all stakeholders understand and comply with the limitations of BGM in critically ill patients or PHS is key to its implementation.**

If an institution or site cannot realistically and reliably comply with these considerations, then it should use other methods of BGM in critically ill patients or in PHS. Many sites use blood gas or non-waived devices instead of glucose meters. **Currently no strip-based glucose meter is cleared by a regulatory body for use with capillary specimens in critically ill patients.** Even if a non-waived device is used for glucose measurement in critically ill patients, many limitations of capillary glucose sampling are physiological and cannot be overcome by changing testing methodology, even with methodology cleared for quantitative glucose measurement without restrictions. **The IFCC WG recommends that all users of BGM in critical care settings and PHS use manufacturer validated meters that are cleared for glucose measurement in those settings, and with demonstrated accuracy and well known performance characteristics as shown in literature studies.** If non-validated meters are being considered, a site must be willing and able to perform formal validation studies.

Since proper verification studies for glucose meters in critically ill patients and PHS are so important, the potential adverse consequences of inappropriate glucose meter use are so great, and the studies can be so complex, looking for ways to share resources and data across testing sites should be explored by the laboratory community as a way to foster best practices and make testing more widely accessible to a variety of settings.

An "institution" could encompass a number of testing sites that are under a single governance structure and will use the same meters, test strips, and testing protocols. A larger site might conduct many of the studies, but each testing site should participate and be able to demonstrate that it can achieve satisfactory performance levels. Part of the verification process is for all stakeholders to experience the real operational requirements of any testing system and to gain understanding of technical, clinical, and logistical variables that may affect results.

Because the verification process of BGM for critically ill patients and PHS will be complex and is so important, the central laboratory should be an essential participant for developing and carrying out the studies in any setting world-wide. In most sites, studies will be under the direction of the central laboratory, but they must always be a collaborative process and must always include actual users and intended use patients. The central laboratory is the best-qualified health care resource to assist in the selection of potential devices, the planning and execution of verification studies, and meter implementation.

The IFCC GMECC WG recognizes that resources are limited for most care sites and BGM verification studies require expertise and a significant resource investment. Given that BGM are so susceptible to significant errors in critically ill patients and in PHS, those studies are essential for any site so that familiarity with the variables and assurance of performance is gained.

In settings where it is too difficult to perform adequate verification studies on glucose meters used for critically ill patients and PHS, there is not adequate central laboratory or other expert assistance with those studies, or there are not reliable resources to maintain quality oversight required for ongoing testing, the WG advises that users select devices or instruments without the limitations of glucose meters and capillary samples. These alternatives would include blood gas instruments, non-waived devices, or central laboratory testing that is expedited for critically ill patients.

In situations where verification studies appear to fail or results do not confirm acceptable performance of glucose meters in PHS, potential users need to reconsider their verification plan, whether they should select another glucose meter to test, or they should use another testing method such as those listed above. They should also consider whether capillary specimens in critically ill patients should be prohibited or whether they should exclude certain care sites and patients from testing by glucose meters.

Finally, the verification process is just one step in the life cycle of a test. The elements of verification should be included in ongoing quality functions such as quality control, new strip lot number checks, periodic comparison of glucose meters to central laboratory testing, proficiency testing or external assessment, introduction of additional glucose meters (of the same type), competency assessment of operators, and problem or safety monitoring to assure best patient outcomes. These elements will be addressed in Terms 3 and 5 of this Work Group's recommendations.