CLINICAL AND LABORATORY STANDARDS INSTITUTE®

2nd Edition

POCT05

Performance Metrics for Continuous Interstitial Glucose Monitoring

This guideline provides consensus guidelines for health care professionals, *in vitro* diagnostic and medical device manufacturers, and regulatory agencies regarding the use of continuous glucose monitoring (CGM) systems and data obtained from CGM systems. This guideline covers how CGM data should be assessed for accuracy, how CGM systems should be assessed for factors that can decrease accuracy, and how CGMs should be operated for optimal performance.

A guideline for global application developed through the Clinical and Laboratory Standards Institute consensus process.

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Performance Metrics for Continuous Interstitial Glucose Monitoring

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Abstract

Clinical and Laboratory Standards Institute guideline POCT05—*Performance Metrics for Continuous Interstitial Glucose Monitoring* provides consensus information for health care professionals, *in vitro* diagnostic and medical device manufacturers, and regulatory agencies regarding how continuous glucose monitoring (CGM) data should be assessed for accuracy, how CGM systems should be assessed for factors that can decrease accuracy, and how CGMs should be operated for optimal performance. This guideline defines and explores multiple aspects of CGM performance, including use cases, point and trend accuracy, evaluation of threshold alerts, system stability and reliability, clinical studies for assessing CGM performance, calibration, measurement traceability, and special considerations such as shelf life, cybersecurity, and product labeling.

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Foreword

Continuous glucose monitoring (CGM) systems are medical devices that measure glucose in the interstitial fluid just under the skin and use algorithms to predict blood glucose values from the measurement. This guideline applies to such devices; however, similar concepts might be applicable to noninvasive or minimally invasive devices. This guideline covers how CGM data should be assessed for accuracy, how CGM systems should be assessed for factors that can decrease accuracy, and how CGM systems should be operated for optimal performance.

The CGM market is experiencing strong growth as accuracy, convenience, sensor duration, and data management capabilities improve and as patients, health care professionals, and payers see the benefits that these devices can provide in the management of glucose levels. Many clinical trials comparing CGM with other blood glucose monitoring methods have demonstrated decreases in mean glycemia, glycemic variability, and the incidence of hypoglycemia. Optimal CGM system performance, as well as practical data comparisons between sensors, can be obtained by following the technical specifications presented in this guideline.

NOTE: To facilitate the readability of this guideline, mg/dL is used as the unit of measure. This preference does not constitute a recommendation for mg/dL over mmol/L. If needed, the following formula can be used to convert mg/dL to mmol/L:

$$\text{mmol/L} = \frac{\text{mg/dL}}{18} \quad (1)$$

Overview of Changes

This guideline replaces the previous edition of the approved guideline, POCT05-A, published in 2008. Several changes were made in this edition, including:

- Extensively revising every chapter
- Adding new chapters that discuss:
  - CGM device use cases
  - Cybersecurity for CGM devices
  - CGM device labeling
- Rearranging subchapters and appendixes, including:
  - Changing stand-alone chapter on lag time to become part of Chapter 8
  - Including text describing establishing measurement traceability in Chapter 4
  - Replacing appendix on clinical studies with Chapter 9
  - Replacing appendix on rate deviation with Subchapters 6.3.1, 6.3.2, and 6.4
- Eliminating appendix covering continuous glucose-error grid analysis

NOTE: The content of this guideline is supported by the CLSI consensus process and does not necessarily reflect the views of any single individual or organization.

Performance Metrics for Continuous Interstitial Glucose Monitoring

Chapter 1: Introduction

This chapter includes:

- Guideline's scope and applicable exclusions
- Background information pertinent to the guideline's content
- Standard precautions information
- Terminology information, including:
  - Terms and definitions used in the guideline
  - Abbreviations and acronyms used in the guideline

1.1 Scope

This guideline provides recommendations for methods used to determine analytical and clinical metrics of continuous glucose monitoring (CGM) as an indicator of blood glucose values. It discusses use cases, point accuracy, trend accuracy, evaluation of threshold alerts, system stability and reliability, clinical studies for assessing CGM performance, calibration, traceability of measurement, cybersecurity, and device labeling.

The intended users of this guideline are *in vitro* diagnostic and medical device manufacturers, regulatory agencies, and health care professionals. This guideline is not intended for use by patients and does not discuss devices that do not meet the definitions of continuous, interstitial, and glucose monitoring.

1.2 Background

The use of self-monitoring of blood glucose (SMBG) devices or glucose meters has led to more normal glucose levels and lower risk of cardiovascular and long-term complications in both type 1 and type 2 diabetes. Patients typically use SMBG devices to test blood glucose levels several times a day to plan diet and/or exercise, to manage diabetes medications, including insulin dosages, and to correct abnormal blood glucose values. Although these devices are easier to use than in the past, many diabetes patients do not comply with SMBG testing at the frequency recommended by their physician because of the cost of testing supplies, the pain of repeated SMBG measurements, the environmental drawbacks of blood and sharps waste, and the overall inconvenience of monitoring.

CGM devices are typically attached to the skin by an adhesive patch or implanted under the skin. Unlike SMBG devices that measure glucose levels in blood (capillary), CGM devices sample interstitial fluid (ISF) from under the skin. Circulating blood glucose distributes into ISF, where it is eventually absorbed by cells. ISF glucose levels are related to although not necessarily the same as blood glucose levels. Depending on physiological circumstances, compared with blood glucose levels, ISF levels may be higher or lower at different times.

CGM devices offer patients the potential to monitor glucose without repeated skin punctures, which are required for SMBG measurements. Although CGM is "continuous," CGM devices may actually only report ISF glucose intermittently, varying from every few seconds to several minutes between measurements. Software inside CGM devices can combine current levels with previous results to predict a future direction of glucose change. CGM instruments can thus display not only a single glucose result but also the direction of glucose change (up, down, or stable), as well as the magnitude of change (amount of glucose change per minute). CGM devices thus offer the potential to predict hypoglycemic or hyperglycemic events before they occur, alert when they do occur, monitor for glucose variations that may not be detectable with SMBG monitoring only a few times a day, and predict future glucose values for determining therapy adjustments. Furthermore, glucose measurements from CGM devices can be combined with insulin-pump dosing information to deliver both up-to-date glucose levels and insulin dosing information on the same screen or incorporated into a closed-loop artificial pancreas system that delivers insulin automatically, based on the continuous measurements.

Currently, true glucose traceability in ISF cannot be established, because reference measurement procedures for glucose are available only for the sample types (matrixes) plasma, serum, and whole blood but not for ISF. For accuracy evaluations, it is important to specify the sampling method and sample type and to use a reference glucose measurement method that is accurate and traceable to a primary standard (eg, an internationally recognized reference material and/or method) (as defined by the *Vocabulaire International de Métrologie [International Vocabulary of Metrology - Basic and General Concepts and Associated Terms] [VIM]*).[1]

CGM data can be classified with a two-dimensional grid for CGM-enabled systems that presents both the types of use cases and the types of device control that a CGM-enabled system can support. Personalized therapies enabled by CGM include insulin therapy management with real-time CGM and automated insulin dosing systems.

Point accuracy of a CGM can be defined as the numerical agreement of a test result between the CGM and a glucose reference method. There is no single metric accepted for evaluating the performance of a CGM. Several metrics are frequently used to describe sensor accuracy in different ways. These metrics include:

- Agreement rates (ie, the percentage of CGM values falling within a specified distance from the reference measurement)

- Agreement when the CGM reading is outside the display range (ie, the concordance of measurements that are specified as "low" or "high" with reference values in these extreme ranges)

Chapter 3: Continuous Glucose Monitoring Use Cases

This chapter includes:

- Description of CGM systems users and CGM data uses
- Descriptions of CGM use cases

3.1 Users of Continuous Glucose Monitoring

The primary users of CGM are patients and clinicians. In fact, the greatest benefit occurs when both the patient and clinician collaborate in short- and long-term diabetes management, such as through cloud-based or in-person data sharing. Table 2 identifies potential use cases and the types of control that can be exerted for data analysis and therapy by software analyzing CGM data. This table presents the types of use cases (including advice to be aware of potentially hazardous situations and/or action) and the types of device control or action that a CGM-enabled system can support (including automated insulin dosing systems or artificial pancreas systems, such as closed loop systems and insulin suspend systems, that use CGM data to adjust insulin dosing autonomously).

Table 2. Potential CGM Use Cases and Types of Control That Can Be Exerted

Type of Control	Use Cases		
	Advice Only	Action Only	Advice and Action
Decision support algorithms	+	–	+
Device control	–	+	+

Abbreviation: CGM, continuous glucose monitoring.

3.2 Situations and End-User Groups Anticipated to Benefit From Continuous Glucose Monitoring

CGM has the potential to be used to better inform and/or manage a number of conditions compared with other methods of blood glucose monitoring. Such use cases include children and adolescents, pregnant women with pregestational type 1 or 2 diabetes or gestational diabetes, the elderly, and adults.

3.2.1 Identification of Clinical Status Informed by Continuous Glucose Monitoring

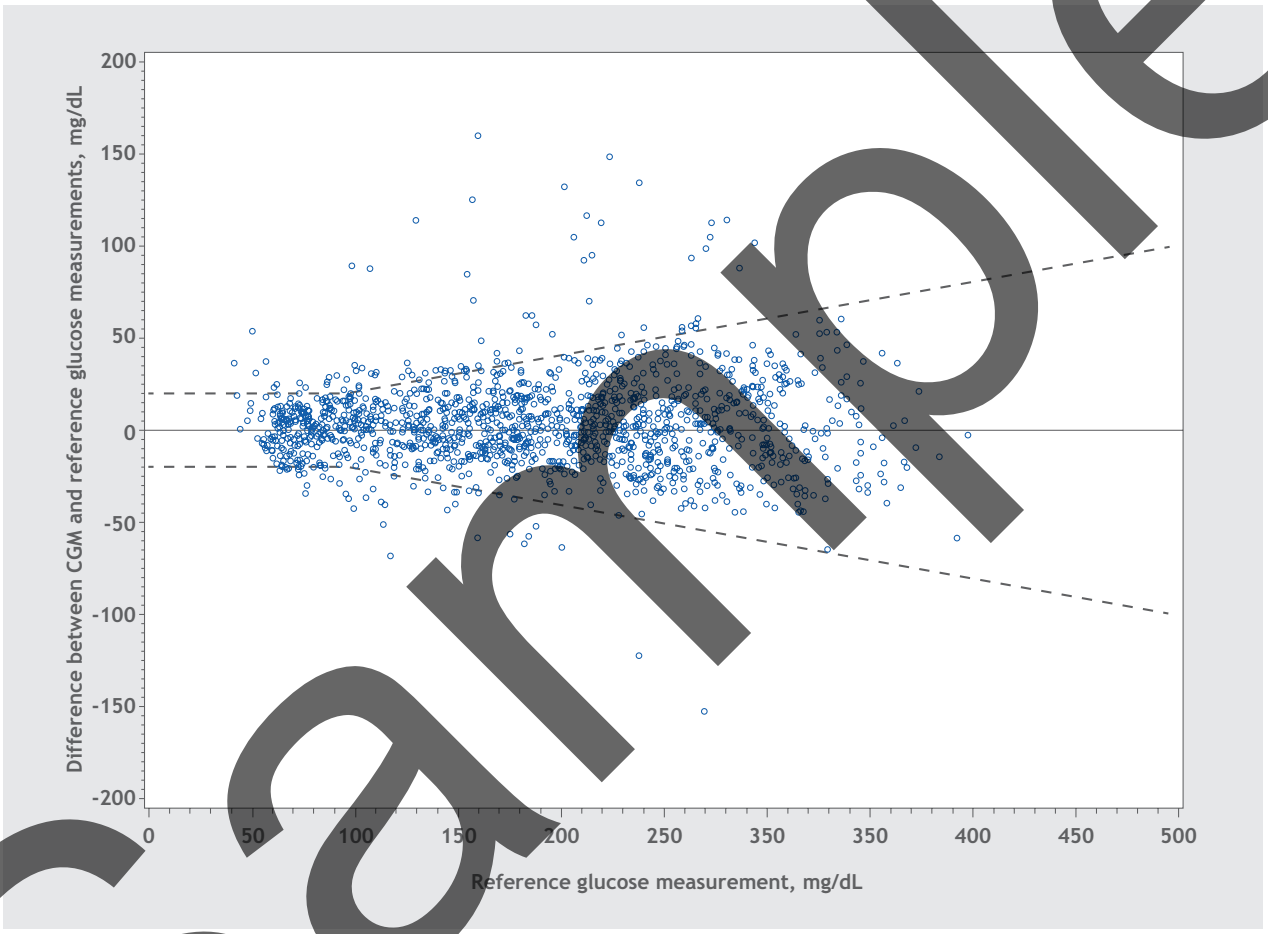
Below is a list of some of the possible situations in which the use of CGM might be considered.

- Detection of night-time hypoglycemia
  - CGM throughout the night can help identify patterns leading to hypoglycemia during sleep and may assist in determining the causes of these patterns.

- Determination of metrics associated with glycemic control, such as time-above-target range, time-in-target range, and time-below-target range, as well as a measure of glycemic variability, such as CV or SD

5.5 Modified Bland-Altman Plot

Accuracy tables are often complemented with a graphical summary of the point differences (see Figure 2). The modified Bland-Altman plot shows the difference between each CGM reading and reference value on the ordinate vs the reference value concentration on the abscissa.[15] The error boundaries used for agreement rates such as the upper and lower 20%/20 mg/dL boundaries can be added to help identify points with poor agreement. In some cases, a regression line is added to summarize bias as a function of concentration. Modified Bland-Altman plots allow identification of any systematic difference between the measurements or possible outliers.

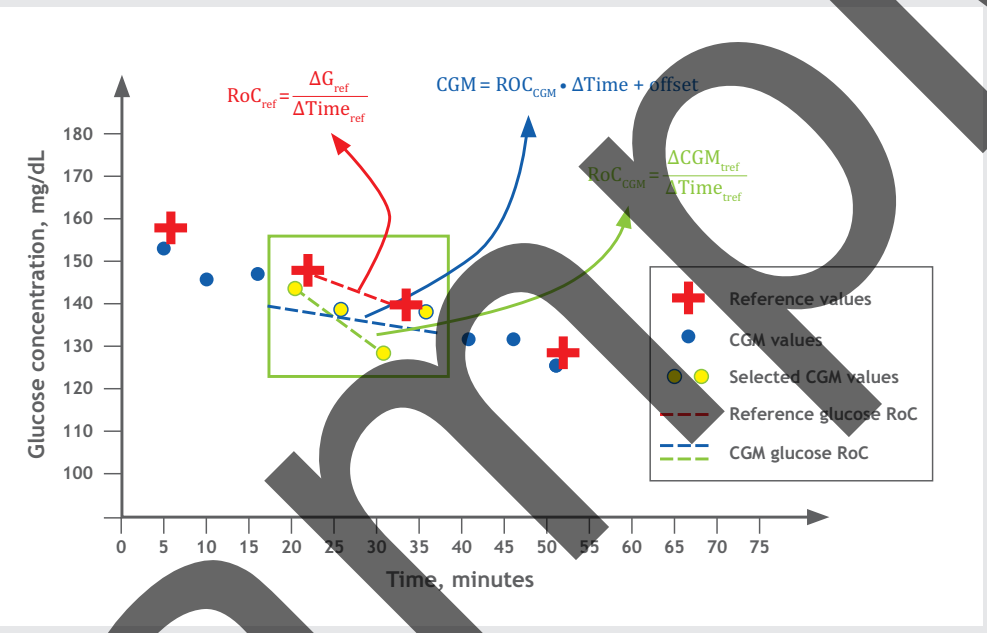


Abbreviation: CGM, continuous glucose monitoring.

Figure 2. Modified Bland-Altman Plot of Differences Between CGM and Reference Glucose Measurements vs Reference Glucose Measurements. Continuous glucose monitoring measurements with reference glucose concentrations between 40 and 400 mg/dL are included, within 20%/20 mg/dL (dashed line) for a cut-point glucose concentration of 100 mg/dL.

reference blood glucose collection times (green dotted line and formula), but such a solution would be more sensitive to high-frequency noise. Trend accuracy should also be evaluated at different glucose RoCs and starting ranges (ie, hypoglycemic, euglycemic, and hyperglycemic).[20]

In the slope-intercept portrayal of a line, the line can be expressed by the formula $y = mx + b$, in which m is the slope and b is the y offset (the value of y when $x = 0$.). In the example in Figure 3, the offset is approximately 162 mg/dL. Although slope or the RoC formula has no offset, as stated above, an equation linking slope with a specific value of the glucose concentration must include an offset. The CGM formula in Figure 3 expresses more than just slope; it links the slope with an absolute value of glucose as portrayed in the y axis.



Abbreviations: CGM, continuous glucose monitoring; RoC, rate of change.

Figure 3. Computing the Best-Fitting Least-Square Line Across Continuous Glucose Monitoring Values. In this example, the offset is approximately 162 mg/dL.

6.2 General Physiological Principles: Blood Glucose Fluctuation Rate

Normal blood glucose fluctuations are physiologically limited in their rate. Assessment of the wide range of glucose readings and rates of change can be achieved in studies that enroll a substantial number of patients with type 1 diabetes. In addition, it may be necessary to actively manipulate glucose concentrations by giving the patients high glycemic index foods, altering their insulin dose, or administering hypoglycemic agents. Appropriate measures to ensure patient safety must be used.

Recent data suggest that glucose-sustained fluctuations up to ± 4 mg/dL per minute over a 15-minute period are reasonable (only 1% of cases may fall outside these boundaries) in type 1 diabetes mellitus, even under exposure to insulin and glucose challenges.[21] Additionally, maximum glucose uptake under high insulinization may

Related CLSI Reference Materials[a]

EP07 **Interference Testing in Clinical Chemistry. 3rd ed., 2018.** This guideline provides background information, guidance, and experimental procedures for investigating, identifying, and characterizing the effects of interferents on clinical chemistry test results.

EP25 **Evaluation of Stability of *In Vitro* Diagnostic Reagents. 1st ed., 2009.** This document provides guidance for establishing shelf-life and in-use stability claims for *in vitro* diagnostic reagents such as reagent kits, calibrators, and control products.

M29 **Protection of Laboratory Workers From Occupationally Acquired Infections. 4th ed., 2014.** Based on US regulations, this document provides guidance on the risk of transmission of infectious agents by aerosols, droplets, blood, and body substances in a laboratory setting; specific precautions for preventing the laboratory transmission of microbial infection from laboratory instruments and materials; and recommendations for the management of exposure to infectious agents.

[a] CLSI documents are continually reviewed and revised through the CLSI consensus process; therefore, readers should refer to the most current editions.

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