This document provides consensus guidelines for health care professionals, in vitro diagnostic (IVD) and medical device manufacturers, and regulatory agencies on how continuous glucose monitor (CGM) data should be: 1) presented; 2) compared between devices; and 3) compared between measurement technologies.

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

Clinical and Laboratory Standards Institute document POCT05-A—Performance Metrics for Continuous Interstitial Glucose Monitoring; Approved Guideline provides a consensus for health care professionals, in vitro diagnostic (IVD) and medical device manufacturers, and regulatory agencies on how continuous glucose monitor (CGM) data should be: 1) presented; 2) compared between devices; and 3) compared between measurement technologies. Terminology is defined for measuring interstitial fluid glucose levels and comparing them to blood glucose levels. The degree of agreement for acceptable technical performance is defined to assess method comparability. This guideline also presents methods for testing CGM performance and interpreting CGM levels. This guideline covers CGM point accuracy and trend accuracy, as well as CGM measurement sensitivity and specificity. The guideline covers device instability due to changes in sensitivity over time. The guideline covers analytical and clinical metrics for establishing the calibration process. It covers approaches for accounting for lag time, which consists of physiologic lag plus process delay. Finally, for CGM measurements, the guideline covers how to use reference materials and establish traceability to a reference system.

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Foreword

This guideline provides a consensus for health care professionals, *in vitro* diagnostic (IVD) and medical device manufacturers, and regulatory agencies on determining analytical and clinical metrics of continuous interstitial glucose monitoring. Continuous interstitial glucose monitors (CGM) are medical devices that measure glucose in the interstitial fluid (ISF) just under the skin. These guidelines are written for such continuous ISF glucose monitoring devices; however, similar concepts might be applicable to noninvasive or minimally invasive devices that apply various forms of optical or acoustic energy or extract ISF. This guideline is not intended for use by patients, and it does not address devices that do not meet the definitions of continuous, interstitial, and glucose monitoring.

Although published protocols have exist for comparing self-management of blood glucose (SMBG) devices to laboratory methods by analyzing differences between glucose levels obtained using SMBG devices and comparative or reference glucose methods, analyzed using portions of the same capillary or venous blood sample, no consensus has been developed for comparing CGM devices to reference methods. This guideline represents a consensus on how continuous glucose monitoring data should be presented and compared between CGM devices and different continuous glucose measurement methodologies on a technical basis. Terminology is defined for measuring ISF glucose levels and comparing them to blood glucose levels. The degree of agreement for acceptable technical performance is defined to allow assessment of method comparability. This guideline also presents methods for testing CGM performance and interpreting CGM levels.

The guideline defines multiple aspects of analyzing CGM performance data. These aspects include: 1) point accuracy; 2) trend accuracy; 3) sensitivity and specificity; 4) device stability; 5) calibration; 6) lag time; and 7) trueness of measurement and device traceability.

Continuous glucose monitor point accuracy can refer to technical agreement or to clinical agreement. The first term refers to numeric agreement of test results between the continuous monitor and a comparative or reference laboratory glucose method. The second term refers to whether the results of the continuous monitor and comparative method would lead to the same patient management decision. Criteria for acceptable agreement must take into account both the technical and the clinical meanings of point accuracy.

Continuous glucose monitor trend accuracy refers to time-dependent characteristics of glucose fluctuations, and in particular, to the short-term or instantaneous rate and direction of change of the glucose concentration. It is desirable that temporal CGM accuracy be evaluated at different glucose rates of change and starting ranges, including hypoglycemia, euglycemia, and hyperglycemia. Furthermore, it is recommended that sensor evaluations be performed in the beginning, middle, and end of sensor life.

Sensitivity and specificity are considered in two different contexts with regard to CGM. The first context is the sensitivity and specificity for the specific analyte, glucose, which can be referred to as analytical sensitivity and specificity. The second context is the sensitivity and specificity for a particular glucose abnormality, such as hypoglycemia or hyperglycemia, which can be referred to as diagnostic or clinical specificity and sensitivity. A CGM may contain a predictive alert feature to improve its diagnostic sensitivity.

Glucose sensor device sensitivity refers to a change in output signal per change in glucose concentration. All glucose sensors change sensitivity over time, and if implanted in the body, CGM sensors may develop instabilities due to changes intrinsic to the sensor and changes at the sensor-biological interface. Analytical recalibration against a well-validated and traceable method should be performed under conditions where systematic drift is suspected.
Calibration metrics that must be specified include: 1) the time from sensor insertion until the time when the sensor data are usable; 2) the number of glucose measurements using the subject’s personal glucose monitoring system that are necessary during the initial calibration period; and 3) the number and frequency of glucose measurements using the subject’s personal glucose monitoring system that are necessary after the initial period and before the end of the sensor lifetime. Sensor systems should not be calibrated at times when they are unlikely to be accurate, such as during periods when the glucose concentration is rapidly changing or when the absolute glucose concentration is in a range where the analytical accuracy is poor and when the sensor output signal is determined to be noisy.

Lag time, which is the time it takes for a device’s glucose reading to become equal to that of the reference value, is comprised mainly of three components: 1) physiologic lag, which reflects the differences in glucose concentrations between venous blood and the medium, such as ISF, which is sampled by the sensor; 2) an instrumental lag that can include, for example, physical lags involving diffusion at the sensor as well as processing delays in which the currently displayed glucose reading may be a weighted average incorporating prior measurements; and 3) processing delay in which the currently displayed glucose reading may be a weighted average incorporating prior measurements. Lag time of the sensor should be disclosed as well as if and/or how it was accounted for in the accuracy evaluations.

The trueness of a measurement result, which is the closeness of agreement between the average value obtained from a large series of test results and an accepted reference value (ISO 3534-1), can be assessed by using reference materials and establishing traceability to a reference system. Measuring glucose in ISF by a CGM and calibrating against plasma or blood glucose by a reference method does not constitute a traceability chain in the meaning of ISO 17511. For some CGMs, traceability can still be established either through split-sample comparisons, a manufacturer’s standing measurement procedure, or in vitro calibration of the CGM in vitro using appropriate calibrators with established traceability.

**Key Words**

Accuracy, calibration, continuous, glucose, lag, metrics, stability, trueness
Performance Metrics for Continuous Interstitial Glucose Monitoring; Approved Guideline

1 Scope

This guideline specifies requirements/recommendations for methods for determining analytical and clinical metrics of continuous interstitial glucose monitoring. It defines the following aspects of continuous glucose monitoring: point accuracy, trend accuracy, sensitivity and specificity, device stability, calibration, lag time, sampling rate, reporting rate, reference material, and reference device traceability.

The intended users of this guideline are health care professionals, in vitro diagnostic (IVD) and medical device manufacturers, and regulatory agencies.

This guideline is not intended for use by the patient.

This guideline does not address devices that do not meet the definitions of continuous, interstitial, and glucose monitoring.

2 Introduction

The use of self-management 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. Self-management of blood glucose devices are typically used to test patients’ blood glucose levels one to four or more times a day to manage diabetes medications, including insulin dosages and correct abnormal blood glucose values. Despite being easier to use than in the past, many patients with diabetes are not compliant with SMBG testing at the frequency recommended by their physician, because of the cost of testing supplies, the pain of repeated fingersticks, and the overall inconvenience of monitoring.

Continuous interstitial glucose monitors (CGM) are medical devices that measure glucose in the interstitial fluid (ISF) just under the skin. Continuous glucose monitor devices are typically attached to the skin by an adhesive patch and can be worn for up to several days. Continuous glucose monitors offer the patients the potential of monitoring their glucose and managing insulin levels without repeated fingersticks. Unlike SMBG devices that measure glucose levels in blood (capillary), CGM samples are from the ISF under the skin. Circulating blood glucose distributes into ISF where it is absorbed by cells. Interstitial glucose levels, therefore, lag behind blood glucose by the amount of time that is required for glucose to diffuse from the circulatory system into ISF, on the order of 3 to 10 minutes or more; additionally, the interstitial glucose may have a bias offset in addition to the lag. However, ISF may be more reflective of the amount of glucose available for cellular metabolism. Although CGM is called continuous, CGM devices actually only sample ISF glucose intermittently, varying from every few seconds to several minutes between measurements. Software within the CGM devices can combine current levels with previous results to predict a future direction of glucose change. Continuous glucose monitors 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). Continuous glucose monitors thus offer the potential to predict hypoglycemic events before they 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.

While published protocols exist for comparing SMBG devices to laboratory methodologies by analyzing differences between glucose levels obtained using SMBG devices and comparative or reference glucose
methods, analyzed using portions of the same capillary or venous blood sample, there is no current consensus on how to compare CGM devices, how to define good agreement given the time lag between blood and ISF levels, or even how to display and interpret the data produced by CGM in a common fashion. A main reason for the lack of consensus is the fact that until now, no sole intended use of CGM devices was defined. The intended use of a device defines the performance specifications and the clinical interpretation of the data.

Despite these issues, this guideline is the first step in reaching a consensus on how CGM data should be presented and compared between devices and different glucose methodologies on a technical basis. Terminology is defined for ISF glucose and its relationship to blood glucose levels, and the degree of agreement for acceptable technical performance is defined to allow assessment of method comparability. Finally, this guideline presents a proposal for clinical interpretation of CGM for utilization in patient care.

Although these guidelines are written for continuous ISF CGM devices, similar concepts might be applicable to noninvasive or “minimally” invasive devices such as those using various forms of spectroscopy, reverse iontophoresis, optical monitoring, acoustic monitoring, or heat conformation.

3 Standard Precautions

Because it is often impossible to know what isolates or specimens might be infectious, all patient and laboratory specimens are treated as infectious and handled according to “standard precautions.” Standard precautions are guidelines that combine the major features of “universal precautions and body substance isolation” practices. Standard precautions cover the transmission of all infectious agents and thus are more comprehensive than universal precautions, which are intended to apply only to transmission of blood-borne pathogens. Standard and universal precaution guidelines are available from the US Centers for Disease Control and Prevention. For specific precautions for preventing the laboratory transmission of all infectious agents from laboratory instruments and materials and for recommendations for the management of exposure to all infectious disease, refer to CLSI document M29.

4 Terminology

4.1 A Note on Terminology

CLSI, as a global leader in standardization, is firmly committed to achieving global harmonization wherever possible. Harmonization is a process of recognizing, understanding, and explaining differences while taking steps to achieve worldwide uniformity. CLSI recognizes that medical conventions in the global metrological community have evolved differently in the United States, Europe, and elsewhere; that these differences are reflected in CLSI, ISO, and CEN documents; and that legally required use of terms, regional usage, and different consensus timelines are all challenges to harmonization. In light of this, CLSI recognizes that harmonization of terms facilitates the global application of standards and deserves immediate attention. Implementation of this policy must be an evolutionary and educational process that begins with new projects and revisions of existing documents.

In order to align the usage of terminology in this document with that of ISO, the term accuracy, in its metrological sense, refers to “closeness of agreement between a measured quantity value and a true quantity value of a measurand,” and comprises both random and systematic effects. Trueness is used in this document when referring to the “closeness of agreement between the average value from a large series of test results and an accepted reference value”; the measurement of trueness is usually expressed in terms of bias. Precision is defined as “closeness of agreement between independent test results obtained under stipulated conditions.” As such, it cannot have a numerical value, but may be determined qualitatively as high, medium, or low. For its numerical expression, the term imprecision is used, which is the “scattering of independent results of measurements obtained under specified conditions.” In addition,
The Quality Management System Approach

Clinical and Laboratory Standards Institute (CLSI) subscribes to a quality management system approach in the development of standards and guidelines, which facilitates project management; defines a document structure via a template; and provides a process to identify needed documents. The approach is based on the model presented in the most current edition of CLSI/NCCLS document HS01—A Quality Management System Model for Health Care. The quality management system approach applies a core set of “quality system essentials” (QSEs), basic to any organization, to all operations in any health care service’s path of workflow (ie, operational aspects that define how a particular product or service is provided). The QSEs provide the framework for delivery of any type of product or service, serving as a manager’s guide. The QSEs are:

- Documents & Records
- Organization
- Personnel
- Equipment
- Purchasing & Inventory
- Process Control
- Information Management
- Process Improvement
- Occurrence Management
- Assessments—External & Internal
- Customer Service
- Facilities & Safety

POCT05-A addresses the QSEs indicated by an “X.” For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.

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Adapted from CLSI/NCCLS document HS01—A Quality Management System Model for Health Care.

Path of Workflow

A path of workflow is the description of the necessary steps to deliver the particular product or service that the organization or entity provides. For example, CLSI/NCCLS document GP26—Application of a Quality Management System Model for Laboratory Services defines a clinical laboratory path of workflow, which consists of three sequential processes: preexamination, examination, and postexamination. All clinical laboratories follow these processes to deliver the laboratory’s services, namely quality laboratory information.

POCT05-A addresses the clinical laboratory path of workflow steps indicated by an “X.” For a description of the other documents listed in the grid, please refer to the Related CLSI Reference Materials section on the following page.

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Adapted from CLSI/NCCLS document HS01—A Quality Management System Model for Health Care.
Related CLSI Reference Materials

M29-A3 Protection of Laboratory Workers From Occupationally Acquired Infections; Approved Guideline—Third Edition (2005). 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.
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