

## Approaches for Improving Glucose Monitor Measurements for Self-Monitoring of Blood Glucose: From Measurement Harmonization to External Quality Assessment Programs

Hubert W. Vesper, Ph.D. and Gary L. Myers, Ph.D.

### Abstract

Self-monitoring of blood glucose (SMBG) is an important component in diabetes management, helping patients to achieve and maintain normal blood glucose levels. The benefit of SMBG depends on the quality of the measurement performed. Therefore, it is important to know the factors affecting the measurements and to assure that the quality of SMBG measurements is at the highest achievable level possible. To accomplish this, all aspects of the measurement procedure need to be taken into consideration. Sources of variability can be related to the monitor itself, its calibration and use, including blood collection. Improving the variability caused by each source requires specifically designed and targeted efforts. Variability related to the monitor can be assessed in studies that minimize other sources of variability. Variability related to monitor calibration can be assessed and minimized through harmonization or standardization programs, while variability related to the use of the monitors can be addressed through patient-oriented assessment and training. The latter may follow procedures similar to external quality assessment (EQA) programs used in clinical laboratory medicine. However, to obtain an optimal impact on patient care, such programs need to have a wide reach and the social and cultural competency to work efficiently with all patients. The EQA approach or approaches that would provide the most benefit to the patient remain to be determined.

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**Author Affiliation:** Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, Georgia

**Abbreviations:** (ADA) American Diabetes Association, (EQA) external quality assessment, (ISO) International Organization for Standardization, (SMBG) self-monitoring of blood glucose

**Keywords:** calibration, device handling, EQA components, external quality assessment, factors affecting measurement variability, harmonization, measurement variability, self-monitoring of blood glucose, specimen collection, standardization

**Corresponding Author:** Hubert W. Vesper, Ph.D., Division of Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, 4770 Buford Hwy, NE (MS F-25), Atlanta, GA 30341; email address [HVesper@cdc.gov](mailto:HVesper@cdc.gov)

## Introduction

**S**elf-monitoring of blood glucose (SMBG) is one of the most important components in diabetes management. The goal of SMBG is to help the patient achieve and maintain blood glucose concentrations as close to those found in nondiabetic individuals as is safely possible.<sup>1</sup> SMBG is performed using hand-held blood glucose monitors. The actual number of glucose monitors used at home by individuals with diabetes is unknown, but it is estimated that 1.0 to 2.5 million individuals with diabetes self-monitor their blood glucose.<sup>2,3</sup> Thus glucose monitors impact the management of diabetes in a large portion of the population. The American Diabetes Association (ADA) recommends SMBG for all insulin-treated individuals with diabetes for<sup>4</sup> (i) achieving and maintaining glycemic control, (ii) preventing and detecting hypoglycemia, (iii) avoiding severe hyperglycemia, (iv) adjusting to changes in lifestyle, and (v) determining the need for initiating insulin therapy in gestational diabetes mellitus.

SMBG helps individuals with type 1<sup>5</sup> or type 2<sup>6</sup> diabetes to take actions that decrease microvascular complications. Further, SMBG can be useful for detecting asymptomatic hypoglycemia and allowing patients to avoid major hypoglycemic episodes.<sup>7</sup> The benefit of SMBG depends on the analytical quality achieved with blood glucose monitors and the actions taken based on these results. Therefore it is important to assure that the quality of SMBG measurements is at the highest achievable level possible. To accomplish this, all aspects of the analytical procedure need to be taken into consideration.

The analytical procedure in SMBG consists of collecting capillary whole blood from a fingerstick or an alternate site on a test strip that contains all the necessary reagents. The glucose concentration in the blood sample is then determined quantitatively by processing the blood-containing strip in the monitor and analyzing the obtained signal using a manufacturer-defined calibration. Finally, a conversion factor is applied and the measurement results are typically displayed as plasma glucose equivalents.

Each component in this process constitutes a potential source of error and requires separate strategies and activities for their assessment, control, and minimization. These components can be categorized into three groups based on the strategies and actions required for minimizing and controlling the variability related to these components:

- Monitor design and its supplies
- Monitor calibration
- Specimen collection and device operation

*Monitors and supplies.* Many types of glucose monitors are available using different technologies for measuring glucose in a blood sample. The meters use reflectance photometry or electrochemistry to measure the rate of the reaction or the final concentration of the reaction products. Over the years, monitors have improved profoundly, helping to decrease operator error through use of “no wipe” strips, automatic commencement of timing after inserting the strip in the instrument, smaller sample volume requirements, larger displays, and additional features to store and manage measurement data. Despite these improvements, factors that may affect glucose measurements remain; these include changes in hematocrit<sup>8</sup>, altitude, environmental temperature or humidity, hypotension, hypoxia, and high triglyceride concentrations.<sup>9</sup> Further, several studies describe variability of monitor results due to lot-to-lot variability of the test strips.<sup>10-12</sup> Some manufacturers address this problem by readjusting their monitor for each strip lot through manual or automated coding systems.<sup>13</sup> Certainly, further studies are needed to better understand these sources of variability. These studies need to be carefully designed to be able to distinguish between variability caused by strip lots and variability caused by other components in the measurement process, such as those related to instrument handling or specimen collection. The outcomes and conclusions of such studies then need to be communicated appropriately to facilitate improvement of the devices as needed.

*Monitor calibration.* Monitors measure glucose in whole blood and normally report values as plasma equivalents to facilitate comparison with assays performed in clinical laboratories and with clinical reference ranges and decision levels that are traceable to a reference method.<sup>7</sup> Therefore, it is important that monitor results are comparable to these reference ranges and decision levels. This is accomplished by making certain that monitors are calibrated in a manner that is comparable to the assay used by the laboratory that provided the reference data. Because of the importance of this aspect, several organizations have developed analytical performance goals describing the allowable or desirable difference between monitors and a reference method. In 1987 the ADA recommended a total error goal of <10% at glucose concentrations of 1.7–22.2 mmol/liter and <15% difference between results obtained with the

monitor and those obtained with a reference method.<sup>14</sup> Based on the knowledge obtained from the Diabetes Control and Complications Trial (DCCT), these performance goals were revised to <5% analytic error.<sup>4</sup> The Clinical Laboratory Improvement Act from 1988 recommends that results with meters should be within 10% of target values or  $\pm 0.3$  mmol/liter, whichever is larger. The Clinical and Laboratory Standards Institute recommends that monitors are  $\pm 20\%$  of laboratory glucose at  $>5.5$  mmol/liter and  $\pm 0.83$  mmol/liter of laboratory glucose if the glucose concentration is  $<5.5$  mmol/liter.<sup>15</sup> The ISO guidelines recommend that 95% of individual glucose results fall within  $\pm 0.83$  mmol/liter of the reference value at concentrations  $<4.2$  mmol/liter and within  $\pm 20\%$  at concentrations  $\geq 4.2$  mmol/liter.<sup>16</sup>

There are several challenges in achieving these performance criteria. Measurement accuracy of clinical devices is commonly assessed by measuring certified reference materials and comparing the measurement results against the true value assigned by a reference method. Because such measurements are highly dependent on the matrix of the sample, such as serum-based matrices or whole blood-based matrices, it is important that the reference material is of the same matrix as the sample used for regular measurements. Glucose monitors use whole blood as the sample matrix. Currently, no whole blood-based reference materials are available to calibrate monitors and assess their accuracy. To overcome this problem, split sample comparison studies can be used. In these studies, a sample is divided into two aliquots and measured by the monitor and the reference method. The literature reports a variety of routine laboratory methods being used for comparison of monitor measurements. Most of these methods are optimized for measuring glucose in plasma or serum and may provide different results when whole blood is used due to specimen-matrix effects.<sup>17</sup> Further, these routine laboratory methods themselves may produce different results compared to an acknowledged reference method. The lack of common calibration of monitors may explain the differences in results observed among monitors.<sup>18,19</sup> Accuracy problems caused by calibration to different points of reference, such as different routine laboratory methods, are commonly minimized through standardization or harmonization efforts. These efforts use reference methods to assess the accuracy of testing systems, which allows establishing metrological traceability. Reference methods for measuring glucose in capillary whole blood have been developed, and procedures that allow split-sample comparison studies are available.<sup>20,21</sup> In this context, it is important to emphasize that assessment of accuracy of the glucose monitors needs to

be performed at different clinically relevant concentration ranges because monitor accuracy can be different, i.e., at hypoglycemic and hyperglycemic concentration ranges. All assessments of accuracy need to be designed in a manner that controls and minimizes all other sources of variability, such as variability caused by the operator or strip lot. Results of accuracy assessments need to be communicated in a manner that facilitates adjustments of monitors as needed.

*Specimen collection and device operation.* Although measurement of blood glucose by glucose monitors is considered a procedure of low complexity requiring minimal operator training and knowledge, the error introduced by the operator, in this case the patient, can be profoundly high. The most commonly cited problems are incorrect use of the test strip, lack of quality control procedures, unclean fingers, and dirty meters.<sup>22-27</sup> Most of these studies also showed that education and continuous training can reduce errors caused by the aforementioned factors and improve measurement performance. The importance of patient error and the need for assessing and improving patient performance are acknowledged and reflected in recommendations by the ADA and ISO. The ADA recommends periodic simultaneous comparisons of a monitor with that of a reference laboratory in combination with patient education. ISO 15197 recommends that a patient performance evaluation should be performed in addition to testing by a medical laboratory technologist.

Different approaches to assess and improve the patient's performance have been described. These approaches perform the assessment and training of the patient either at the health care facility<sup>22,23,26,28</sup> or at the patient's home.<sup>25</sup> They all follow the general principles of external quality assessment (EQA) programs, which consist of an independent assessment of the equivalence among results and a follow-up component to help participants improve in their performance. Initially, EQA programs were developed and successfully used to improve laboratory measurements. EQA allows participants to identify problems with their testing process and provides improvement opportunities. It further increases awareness of quality benefits.

Key components in EQA programs are:

- appropriate commutable materials that are stable for the period of the exercise,
- regularity and frequency of testing, and
- data analysis, including performance evaluation and training.

Currently, no commutable control material is available that can be used by all monitors for EQA purposes. Therefore, different materials would be needed and participants would need to be classified into peer groups by monitor and control materials used. These materials would be sent to the patient for testing and the testing results would be reported back to the EQA provider who evaluates the results and provides feedback and training to the patient. One challenge here would be obtaining adequate numbers of participants in each peer group to perform tests that provide results with sufficient statistical power. Another approach would use split-sample comparison studies. Here, the testing would be performed at the health care facility using actual patient samples that are measured by the patient and by the routine laboratory device as the comparison method. Feedback and training would be provided immediately by the health care provider.

When the EQA materials are used to assess the accuracy of the monitors in addition to the performance of the patient, the values assigned to the materials should be traceable to a higher metrological order of reference. This is accomplished through value assignments performed by accredited reference measurement laboratories. To assure the highest quality of service, and thus the optimal outcome for the patient, the EQA program should be able to distinguish between instrument problems and operator problems. Further, the EQA program should be appropriately accredited.

Such EQA programs can only improve patient performance and probably point out problems related to instrument design and calibration. Thus, EQA programs cannot substitute other efforts related to harmonization or instrument performance.

In summary, SMBG will continue to have a major benefit for individuals with diabetes. This benefit can be increased through continuous efforts to improve the glucose monitor measurements. The efforts need to be targeted at the specific aspects that are intended to be improved. Harmonization efforts and further technical improvements of the monitors and their supplies will help to create the basis for improved measurements and tools and procedures to implement harmonization efforts and assess monitor performance. However, continuous assessment and training of the patient are equally important and challenging. Different approaches reaching from informal patient training to formalized EQA programs are technically possible. Studies describing existing EQA approaches are all performed using a fairly

small patient population. To achieve an optimal impact on patient care, such programs need to be able to reach all or a major portion of individuals with diabetes and need to have the social and cultural competency to work efficiently with all patients. The EQA approach or approaches that would provide the most benefit to the patient remain to be determined.

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#### Disclosure:

Use of trade names and commercial sources is for identification only and does not constitute endorsement by the U.S. Department of Health and Human Services or the Centers for Disease Control and Prevention. The findings and conclusions in this report are those of the authors and do not necessarily represent the views of the Centers for Disease Control and Prevention/the Agency for Toxic Substances and Disease Registry.

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