Submitting Continuous Glucose Monitoring Data in Clinical Trials

Guidance for Industry

Technical Specifications Document

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TABLE OF CONTENTS

1.0 Introduction 1
1.1. Purpose 1
1.2. Background 1
1.3. Scope 3
1.4. Relationship to Other Documents 4
2.0 Relevant Acronyms 4
3.0 Overview of Dataset Specifications 5
3.1 SDTM Specifications 5
3.1.1 Laboratory Test Results Dataset 5
3.1.1.1 General Considerations 6
3.1.1.2 Handling of Missing SDTM Epoch-Level Data 6
3.1.2 Trial Summary Dataset 8
3.1.3 Datasets for CGM DHT-Level Review 8
3.1.4 Disposition Dataset 10
3.2 ADaM Specifications 10
3.2.1 ADaM Epoch-Level Dataset 11
3.2.1.1 General Considerations 11
3.2.1.2 Windowing of Epoch-Level Assessment Timepoints 13
3.2.1.3 Handling of Missing ADaM Epoch-Level Data 15
3.2.2 ADaM Intermediate Summary Dataset 16
3.2.3 ADaM Final Analysis Dataset 16
3.2.3.1 General Considerations 17
3.2.3.2 Handling of Missing ADaM Final Analysis Data 18
3.2.4 ADaM Paired Glucose Analysis Dataset 19
4.0 Specifications for Tables and Figures 21
5.0 References 22
6.0 Appendix 23
6.1 Example SDTM Laboratory Test Results Dataset (LB Dataset) 23
6.2 Example ADaM CGM Epoch-Level Dataset (ADCGM Dataset) 27
6.3 Example ADaM Final Analysis Dataset (ADCGMEN Dataset) 36
6.4 Example ADaM Paired Glucose Analysis Dataset (ADGLUCPR Dataset) 37
6.5 Example Tables and Figures 40

TABLE OF TABLES

Table 1. Specifications for a Subset of LB Variables **6**
Table 2. Recommended LB Representation of Missing CGM Epoch-Level Data **8**
Table 3. Specifications for a Subset of ADCGM Variables **11**
Table 4. Specifications for a Subset of ADCGMEN Variables **17**
Table 5. Specifications for ADGLUCPR Variables **20**
Table A1. SDTM Epoch-Level Dataset Example **25**
Table A2. ADCGM Dataset Example **29**
Table A3. Final Analysis Dataset Example **36**
Table A4. ADGLUCPR Dataset Example **39**
Table A5. Data Completeness Summary by Treatment Arm and Analysis Visit **41**
Table A6. Missing Data Summary by Treatment Arm and Reason **41**

TABLE OF FIGURES

Figure 1. Example DHT Data Flow for CGM **2**

Contains Nonbinding Recommendations

Submitting Continuous Glucose Monitoring Data in Clinical Trials

Guidance for Industry
Technical Specifications Document[1]

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

1.0 INTRODUCTION

1.1. Purpose

This document provides technical specifications for submitting continuous glucose monitoring (CGM) data in clinical trials to support a marketing application for a drug or biological product.

In general, FDA's guidance documents do not establish legally enforceable responsibilities. Instead, guidances describe the Agency's current thinking on a topic and should be viewed only as recommendations, unless specific regulatory or statutory requirements are cited. The use of the word *should* in Agency guidances means that something is suggested or recommended, but not required.

1.2. Background

A CGM digital health technology (DHT) is a system that continuously and passively collects glycemic data by measuring glucose levels in the interstitial fluid and can provide access to near real-time glucose measurements and trend information regarding glucose levels throughout the day[2] CGM data can consist of epoch-level data, intermediate summary data, final analysis data, and other CGM data. An example of data flow for CGM is provided in Figure 1.

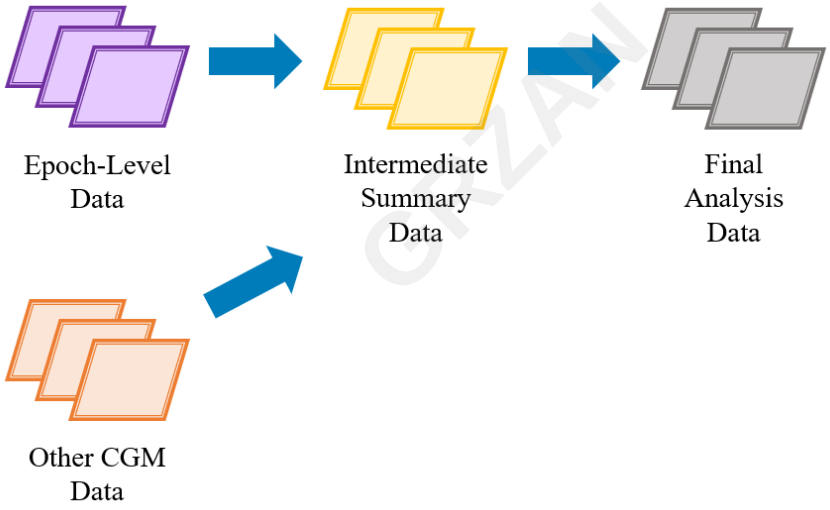
For CGM, the *epoch-level* data refers to the frequency (i.e., sampling rate) of the granular CGM readings (i.e., the glucose levels) reported within the dataset based on the epoch length (e.g., every 1-minute, 5 -minute, or 15 -minute, depending on the make and model of the CGM DHT).

[1] This guidance has been prepared by the Office of Biostatistics in the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research at the Food and Drug Administration. You may submit comments on this guidance at any time. Submit comments to Docket No. FDA-2018-D-1216 (available at https://www.regulations.gov/docket?D=FDA-2018-D-1216) (see the instructions for submitting comments in the docket).

[2] See FDA's draft guidance for industry *Diabetes Mellitus: Efficacy Endpoints for Clinical Trials Investigating Antidiabetic Drugs and Biological Products* (May 2021). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at https://www.fda.gov/RegulatoryInformation/Guidances/default.htm.

The data flow for CGM may include intermediate summary data as shown in Figure 1. When submitted, intermediate summary data is generated from the epoch-level data and bridges the epoch-level data and the final analysis data. The final analysis data represent the dataset(s) used to evaluate the CGM-derived endpoints and for other analyses prespecified in the statistical analysis plan (SAP). For example, depending on the CGM-derived pre-specified study endpoints (e.g., time in range (TIR) during the last two weeks of the study), 1) the epoch-level dataset may report CGM readings every five minutes, 2) the intermediate summary dataset may report daily or weekly totals, and 3) the final analysis dataset may report averages or other summary metrics for the pre-specified endpoints at specific time frames (e.g., a two-week average). Alternatively, epoch-level data may flow directly into the final analysis data when intermediate summaries are not produced. In Figure 1, "other CGM data" refers to additional collected data that are separate from the epoch-level data, such as CGM DHT characteristics (e.g., manufacturer and model), software version(s), and other participant interaction data.

Figure 1. Example DHT Data Flow for CGM



Throughout this document, the following terminology is used:

- 'CGM reading' refers to epoch-level data where a glucose level is provided.
- 'Epoch-level data' refers to CGM readings as well as other data outputted at the epoch-level, such as error codes.
- 'Other CGM data' refers to the additional data collected separate from the epoch-level data as described in section 1.2 Background.
- 'CGM DHT' refers to the CGM system described in section 1.2 Background.

- 'CGM-derived endpoint' refers to the study-specific outcome measure that is calculated using the data collected by the CGM DHT.

- 'CGM data' is a general term that refers to all datasets within the CGM data flow.

1.3. Scope

This document provides specifications for the submission of Clinical Data Interchange Standards Consortium (CDISC) Study Data Tabulation Model (SDTM) and Analysis Data Model (ADaM) datasets and specifications for recommended tables and figures. These technical specifications aim to provide general guidelines for standardized content and structure to facilitate FDA review of the marketing application that the submitted data and analysis outputs are intended to support. The SDTM and ADaM dataset specifications outlined in section 3.0 Overview of Dataset Specifications are not prescriptive and are not intended to include an exhaustive list of all datasets, variables, and controlled terminologies to be submitted for FDA review. Further, the recommended tables and figures within section 4.0 Specifications for Tables and Figures may not comprise all information needed to support FDA review of a marketing application.

This document does not pertain to the following:

1) The proposed interpretation and use of outputs generated by a CGM DHT within the context of a specific clinical trial.

2) The verification or validation of the CGM DHT. Refer to guidance for industry *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations* (December 2023).

In addition, this document does not include technical specifications for closed-loop systems where the CGM DHT is coupled with an insulin pump and insulin is administered using an algorithm based on collected CGM readings. Further, this document does not include standardized definitions for CGM-derived endpoints. Sponsors should provide clear definitions of all CGM-derived endpoints within the study protocol with corresponding rationale. For example, this may include how a hypoglycemic event is defined and classified based on the CGM data and, if relevant, the proposed duration used to identify the event. These technical specifications should be referenced when a CGM DHT is used within a clinical trial to evaluate CGM-derived endpoints.

The specifications provided in this document are pursuant to discussions with FDA and may vary by clinical drug or biologic development program and the clinical trial therein. The CGM DHT used to collect study data and corresponding analyses should be discussed with FDA as early as possible in a clinical drug or biologic development program (e.g., at the End of Phase 2 Meeting). Sponsors are strongly encouraged to use the resources described in section 1.4 Relationships to Other Documents and to seek Agency input for confirmation and clarification as needed. Sponsors should consult with the Agency to determine which requested displays defined in section 4.0 Specifications for Tables and Figures apply to the CGM data used to support the marketing application.

1.4. Relationship to Other Documents

These technical specifications have been drafted in accordance with the business rules and assumptions outlined in the CDISC SDTM,[3] the SDTM Implementation Guide (SDTMIG),[4] the SDTMIG for Medical Devices (SDTMIG-MD),[5] the ADaM,[6] and the ADaM Implementation Guide (ADaMIG). As new versions of the models and implementation guides become available, these technical specifications may be updated to maintain alignment. In addition, the FDA Study Data Technical Conformance Guide (sdTCG)[7] provides general specifications and recommendations for submitting datasets using the SDTM and ADaM standards. Sponsors should review the FDA Data Standards Catalog[8] to ensure data submissions follow FDA-supported standards.

In addition, sponsors should reference the following:

- Draft guidance for industry *Diabetes Mellitus: Efficacy Endpoints for Clinical Trials Investigating Antidiabetic Drugs and Biological Products* (May 2023)[9]

- Guidance for industry *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations* (December 2023)

- CDISC Controlled Terminology[10]

2.0 RELEVANT ACRONYMS

Abbreviation	Description
ADaM	Analysis Data Model
ADaMIG	Analysis Data Model Implementation Guide
ADRG	Analysis Data Reviewer's Guide
BDS	Basic Data Structure
CDISC	Clinical Data Interchange Standards Consortium
CBER	Center for Biologics Evaluation and Research
CDER	Center for Drug Evaluation and Research
CDRH	Center for Devices and Radiological Health
CGM	Continuous Glucose Monitor
cSDRG	Clinical Study Data Reviewer's Guide
CSR	Clinical Study Report

[3] More information is available at CDISC's SDTM web page: https://cdisc.org/standards/foundational/sdtm.
[4] More information is available at CDISC's SDTMIG web page: https://cdisc.org/standards/foundational/sdtmig.
[5] More information is available at CDISC's Medical Devices web page: https://www.cdisc.org/standards/foundational/medical-devices
[6] More information is available at CDISC's ADaM web page: https://cdisc.org/standards/foundational/adam.
[7] More information is available at FDA's Study Data Standards Resources web page: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.
[8] More information is available at FDA's Study Data Standards Resources web page: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.
[9] When final, this guidance will represent the FDA's current thinking on this topic.
[10] More information is available at NCI's web page: https://datascience.cancer.gov/resources/cancer-vocabulary/cdisc-terminology.

Abbreviation	Description
DHT	Digital Health Technology
DI	Device Identifier
FDA	Food and Drug Administration
FD&C Act	Federal Food, Drug, and Cosmetic Act
NCI EVS	National Cancer Institute Enterprise Vocabulary Services
PI	Production Identifier
SAP	Statistical Analysis Plan
sdTCG	Study Data Technical Conformance Guide
SDTM	Study Data Tabulation Model
SDTMIG	Study Data Tabulation Model Implementation Guide
SDTMIG-MD	Study Data Tabulation Model Implementation Guide for Medical Devices
SMBG	Self-Monitoring Blood Glucose
SMPG	Self-Monitoring Plasma Glucose
TIR	Time in Range
UDI	Unique Device Identifier

3.0 OVERVIEW OF DATASET SPECIFICATIONS

These dataset specifications detail the CDISC datasets to support the collected CGM data and analysis data. Sponsors should implement the CDISC SDTM standard when submitting data collected during the clinical trial and the CDISC ADaM standard when submitting analysis data. As documented in the FDA sdTCG,[11] both SDTM and ADaM datasets should be accompanied by informative metadata provided in a compliant data definition file (i.e., Define-XML) and with a Clinical Study Data Reviewer's Guide (cSDRG) and an Analysis Data Reviewer's Guide (ADRG), respectively. Standard CDISC Controlled Terminology[12] developed and maintained by CDISC and National Cancer Institute Enterprise Vocabulary Services (NCI EVS) should be used where applicable, and codelists may be extensible by adding controlled terminology that is not previously defined. Sponsor-extended codelists and use of alternate (e.g., non-CDISC or sponsor-defined) terminologies should be indicated in the study metadata (e.g., Define-XML file, cSDRG). In addition, software programs (source code) used to create the ADaM CGM datasets and to analyze the CGM data should be submitted with the marketing application.

3.1 SDTM Specifications

This section details the SDTM specifications for (1) the CGM epoch-level data submitted within the Laboratory Test Results (LB) dataset, (2) the Trial Summary (TS) dataset, (3) additional datasets to support CGM DHT-level review, and (4) the Disposition (DS) dataset.

3.1.1 *Laboratory Test Results Dataset*

The epoch-level data provides continuous CGM readings as described in section 1.2 Background, where the frequency of the reported timestamps is based on the sampling rate of the

[11] More information is available at FDA's Study Data Standards Resources web page: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.
[12] More information is available at NCI's web page: https://datascience.cancer.gov/resources/cancer-vocabulary/cdisc-terminology.

CGM DHT. The submitted epoch-level dataset is represented using the SDTM Laboratory Test Results (LB) domain specifications. Note that it may be necessary to split the LB dataset depending on dataset size constraints as described by FDA's sdTCG.[13]

3.1.1.1 General Considerations

CGM data within the LB dataset contain the epoch-level data as collected for individual patients at distinct assessment timepoints (e.g., every 1-minute, 5-minute, or 15-minute), where the epoch length depends on the make and model of the CGM DHT. When system errors result in excess or fewer data collected than expected (e.g., 288 records per day are expected if the epoch length is 5 minutes or 1440 records per day are expected if the epoch length is 1 minute), an explanation should be provided. The subset of standard LB variables presented in Table 1 is shown to clarify how variables should be completed for the epoch-level data to foster consistency and standardization across industry. An example LB dataset is provided in Appendix 6.1.

Table 1. Specifications for a Subset of LB Variables

Variable Name	Variable Label	Type	Comments
LBSTAT	Completion Status	Char	This is populated as 'NOT DONE' for records in the LB dataset where the CGM reading is empty/null. Conversely, LBSTAT is empty/null when a CGM reading exists in LBORRES.
LBREASND	Reason Not Performed	Char	This is used in conjunction with LBSTAT when LBSTAT = 'NOT DONE' to describe why a CGM reading is empty/null when collected by the CGM DHT (See section 3.1.1.2 Handling of Missing SDTM Epoch-Level Data).
LBMETHOD	Method of Test or Examination	Char	For CGM epoch-level data, LBMETHOD = 'CGM'.
LBDTC	Date/Time of Specimen Collection	Char	Date/Time of individual epoch-level assessment timepoints in ISO 8601 datetime format.

Additional Considerations:

Additional CGM epoch-level data collected beyond what is specified in the SDTM LB domain specifications should be submitted either as additional rows with relevant LBTEST and LBTESTCD values within the LB dataset or within a Supplemental Laboratory Test Results (SUPPLB) dataset. Additional content is dependent on the CGM DHT used, and if needed for analysis, should be provided within the applicable ADaM dataset.

3.1.1.2 Handling of Missing SDTM Epoch-Level Data

FDA review will consider the reasons for and prevalence of missing CGM readings. This section expands upon the missing data considerations presented in FDA's guidance for industry *Digital Health Technologies for Remote Data Acquisition in Clinical Investigations* (December 2023).

[13] More information is available at FDA's Study Data Standards Resources web page: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

Sponsors should make every effort to minimize the overall amount of missing CGM data within a study. Missing CGM readings should be represented within the LB dataset with the reason for missingness captured under 'Reason Not Performed' (LBREASND) when collected by the CGM DHT at the epoch level. Ideally, the LB dataset should contain one record per CGM reading per patient per epoch for the entire planned, protocol-specified period of CGM DHT wear (e.g., the duration of the trial) up until discontinuation (from the study or from CGM) or death; however, this may not be feasible within the LB dataset if the epoch-level data presented in the LB dataset only contains epochs where a CGM reading or an error code is collected and transmitted by the CGM DHT. For example, if a patient removes the sensor and does not replace it, the affected epochs may not be present within the LB dataset because no data is collected by the CGM DHT. In this case, epoch-level data to represent intermittent missing data should be provided in the ADaM epoch-level dataset as presented in section 3.2.1 ADaM Epoch-Level Dataset.

Epoch-level data related to the initialization, or warmup, period (when a CGM sensor session first starts after the initial placement) may be collected and transmitted by the CGM DHT. During this period, CGM readings are typically blinded and not recorded while the CGM DHT performs initialization, which may cause the readings to appear as 'missing' in the dataset. Once the CGM warmup period is complete, the CGM will start recording readings. Warmup can last several minutes or hours, depending on the make and model of the CGM DHT used in the study. When collected, epoch-level data related to the warmup period are provided within the LB dataset. Including these epoch-level data from the warmup period within the dataset provides transparency as to the reason CGM readings appear to be missing and allow for a participant's complete sensor session beginning with sensor insertion to be represented within the dataset.

A single participant may have multiple warmup periods within the epoch-level dataset, depending on the number of sensor replacements specified in the protocol. Further, the number of distinct warmup periods may vary by participant depending on the total number of sensors that are replaced for each participant. For example, if a participant has additional sensor replacements beyond what is specified in the protocol due to multiple early sensor termination events while others wear each sensor for its maximum lifetime, the participant will appear to have more missing CGM readings than other participants. Reporting warmup period information within the LB dataset allows for an assessment of imbalance in warmup periods between participants and treatment arms.

Table 2 provides scenario-specific recommendations for displaying records for missing CGM readings within the LB dataset, where the human-readable description of the error code outputted by the CGM DHT is provided within LBREASND. Additional error code information needed to fully interpret the descriptions should be provided within the study metadata documentation (e.g., the SDTM Define-XML file or the cSDRG) as needed. Note that there may be other scenarios in which readings are missing in addition to those listed in Table 2.

Table 2. Recommended LB Representation of Missing CGM Epoch-Level Data

Scenario	Recommended Representation in LB Dataset
CGM readings are completely missing due to **nonwear** of the CGM DHT, for example if the sensor is accidentally or purposely removed or if the sensor is not replaced immediately between sensor sessions.	Rows for the missing epochs are excluded from the LB dataset.
CGM readings are missing due to the **warmup period** that occurs for a period of epochs after sensor insertion during initialization of the CGM DHT.	When collected by the CGM DHT, the rows for the missing epochs should include: • LBSTAT = 'NOT DONE' • LBREASND contains the human-readable description of the error code generated by the CGM DHT (e.g., 'Warmup period', 'Sensor not calibrated', 'Calibration failure', 'Sensor termination', 'Data transmission failure', 'Data upload failure'). If not collected by the CGM DHT, the rows for the missing epochs are excluded from the LB dataset.
CGM readings are blinded or not collected due to **early sensor termination**. Examples include partial or full sensor detachment when a sensor is dislocated or internal damage to the sensor electrode.	
CGM readings are missing due to **data transmission issues**, for example gaps in wireless transmission causing data loss.	
CGM readings are missing due to **file corruption issues**, for example file corruption causing failure to upload data to the server.	

Missing epoch-level data in the ADaM ADCGM dataset are presented in section 3.2.1.3 Handling of Missing ADaM Epoch-Level Data. An example of missing data within the LB dataset is provided in Appendix 6.1.

3.1.2 *Trial Summary Dataset*

Data related to the trial summary should be stored in the TS dataset. Of particular interest to FDA is the frequency with which these technical specifications in this guidance are used to create and submit CGM data. Per the FDA sdTCG,[14] sponsors may include the following parameters and associated value in the TS dataset to indicate that these technical specifications were used for the study:

- TSPARAMCD = 'FDATCHSP'
- TSPARAM = 'FDA Tech Spec'
- TSVAL = 'CGM Technical Specifications Guidance v1.0'

3.1.3 *Datasets for CGM DHT-Level Review*

The submission of additional data not provided within the SDTM epoch-level dataset is recommended to enable CGM DHT-level review and analysis and to enhance traceability. These data include information about the interactions between the CGM DHT and the participant. These data include other CGM data not already provided within the SDTM epoch-level dataset such as CGM DHT characteristics, identifier information, settings, software version(s), and other participant interaction data. Within the context of CGM, these datasets may include the datasets

[14] More information is available at FDA's Study Data Standards Resources web page: https://www.fda.gov/industry/fda-resources-data-standards/study-data-standards-resources.

described below. Note however that other datasets should be included in the submission as needed.

CGMs are class II medical devices subject to FDA's unique device identification system requirements, including assignment of a unique device identifier (UDI) as defined in 21 CFR 830.3. A **UDI** is a unique numeric or alphanumeric code that adequately identifies a medical device through its distribution and use and consists of:

- **Device identifier (DI)**, a mandatory, fixed portion of a UDI that identifies the labeler and the specific version or model of a device.
- **Production identifier (PI)**, a conditional, variable portion of a UDI that identifies one or more of the following when included on the label of a device:
    - Lot or batch number within which a device was manufactured (for devices that incorporate software, 'lot or batch' is defined to include the software version);
    - Serial number of a specific device;
    - Expiration date of a specific device;
    - Date a specific device was manufactured; and
    - Distinct identification code required by § 1271.290(c) for a human cell, tissue, or cellular and tissue-based product (HCT/P) regulated as a device.[15]

When CGM is used in a study, it is encouraged that a dataset containing the FDA-required UDI be submitted. This dataset serves as a single location to record the identifiers or characteristics used to uniquely identify each CGM DHT used in a study. Within the dataset, Sponsor Device Identifier (SPDEVID) variable should be populated by the UDI (both DI and PI portions) which represents the single identifier for each CGM sensor and is used to link data. This UDI is especially useful when the CGM sensor is replaced multiple times by the participant throughout the study as specified in the protocol. The DI portion of the UDI identifies the version or model of the CGM. If the version or model changes, a new DI would be assigned. The PI elements of the UDI capture the serial number, software version (in the lot or batch variable), manufacturing date and expiration date, if applicable.

As shown in Table 3. Specifications for a Subset of ADCGM Variables, SPDEVID is encouraged to be submitted within the ADaM ADCGM dataset. A separate SPDEVID value for each sensor session under which corresponding epoch-level data is collected by the CGM DHT is recommended to enable sensor-level analysis directly within the ADCGM dataset. To facilitate review, a dataset that contains all distinct pairs of SPDEVID and Unique Subject Identifier (USUBJID) values observed in the study data should be submitted. CGM data depicting the properties and settings of a CGM DHT such as software name and/or version should be submitted in separate findings dataset(s). Software version should be captured as part of the PI

[15] See 21 CFR 830.3. For additional information on UDIs, see the FDA webpage, "UDI Basics | FDA."

lot or batch data element. Example properties captured for a CGM DHT include alarms used to indicate hyper- or hypoglycemia and software name and/or version. Note that representing properties and settings of each CGM DHT are useful within a dataset when there are differences observed across CGM DHTs, participants, and/or assessment timepoints. Alternatively, when properties and settings are identical throughout the study, these details may instead be presented directly in the study protocol.

CGM data depicting events that occur to a CGM DHT during the study should be submitted. Documentation of these events is especially useful when they can affect the CGM readings collected by the CGM DHT or the interpretation of the CGM results. Relevant information related to such events may include date/time of each sensor insertion, date of data upload for a sensor session, CGM DHT or software upgrades or downgrades, error codes generated by the CGM DHT that are not accounted for within the epoch-level dataset, and other CGM DHT issues or errors that result in data being excluded from the epoch-level dataset (e.g., loss of connectivity, data upload failure). Missing data due to the CGM DHT that is not provided in the epoch-level dataset should be reported.

When using CGM in a clinical investigation, it is recommended that sponsors adequately plan for changes that could occur during the trial, such as CGM upgrades. When feasible, the CGM model should be the same throughout the trial for all participants. Sponsors should have an adequate number of CGM DHTs to start and complete the trial. Different models of CGM DHTs may have different analytical performance, which may complicate the analysis of CGM data collected during the trial. Different CGM models may also have different features such as sensor replacement frequency and capability to backfill missed CGM readings, which can result in differences in the frequency of missing data. In some instances, minor changes may be made between versions within a single CGM model line that do not impact performance. Thus, it is encouraged that each participant uses the same CGM model and version throughout the trial unless the performance and feature set is determined to be identical between the models or versions. Details on CGM DHT changes that occur during the trial, including the UDI, justification for changes and plans for addressing differences caused by a change, should be provided in the study protocol and the SAP.

3.1.4 *Disposition Dataset*

Discontinuation-related disposition events for a participant may include discontinuation from a treatment, discontinuation from a study, or discontinuation from a certain segment(s) of a study. When CGM is used in a study, it is recommended that the date of permanent discontinuation from the CGM DHT be collected in a structured manner and presented within the DS dataset. This date can then be referenced into the ADaM ADCGM dataset as described in section 3.2.1 ADaM Epoch-Level Dataset.

3.2 ADaM Specifications

This section provides specifications for the ADaM datasets containing analysis-ready CGM data. ADaM datasets included within this section include the analysis datasets outlined in the CGM data flow shown in section 1.2 Background: the epoch-level data, intermediate summary data (if

applicable), and final analysis data. In addition, specifications are provided for paired glucose datasets that join the CGM and non-CGM glucose data.

3.2.1 *ADaM Epoch-Level Dataset*

In addition to epoch-level data submitted within the SDTM LB dataset, epoch-level data for CGM should be submitted using the ADaM dataset (herein referred to as the ADCGM dataset). An ADCGM dataset may be created to bridge the gap between the epoch-level data in the SDTM LB dataset and the final analysis data described in section 3.2.3 ADaM Final Analysis Dataset. When created, the ADCGM dataset is derived from epoch-level data in the SDTM LB dataset presented in section 3.1.1 Laboratory Test Results Dataset in conjunction with other SDTM and ADaM data.

Because the ADLB dataset is historically a large dataset in comparison to other ADaM datasets, a standalone ADCGM dataset should be submitted to report the ADaM epoch-level data, rather than submitting epoch-level data within an ADaM dataset that also summarizes other non-CGM laboratory results. Further, creating the standalone ADCGM dataset allows for analysis variables not relevant to the analysis of standard laboratory test results to be fully utilized for epoch-level data and vice versa.

3.2.1.1 General Considerations

The ADCGM dataset follows the ADaM Basic Data Structure (BDS) and presents epoch-level data at the same frequency as the SDTM LB dataset (e.g., every 1-minute, 5-minute, or 15-minute, depending on the make and model of the CGM DHT). Table 3 contains specifications for a subset of ADCGM variables, some of which are standard ADaM BDS variables (included here to clarify how they should be completed for epoch-level data to foster consistency and standardization across industry as well as traceability) and some of which are newly defined. Table 3 does not include all ADCGM variables to may be submitted within the BDS dataset. An example ADCGM dataset is provided in Appendix 6.2.

Table 3. Specifications for a Subset of ADCGM Variables

Variable Name	Variable Label	Type	Comments
ADTM	Analysis Datetime	Num	Datetime of individual epoch-level assessment timepoints using an appropriate display format.
AVISIT or ATPT	Analysis Visit or Analysis Timepoint	Char	The primary analysis timing variable (e.g., AVISIT, ATPT, or another analysis timing variable) used in the study to which the individual epoch-level assessment timepoints are mapped (See section 3.2.1.2 Windowing of Epoch-Level Assessment Timepoints).
SPDEVID	Sponsor Device Identifier	Char	This should be populated by the FDA-required UDI which represents the single identifier for each CGM sensor used to produce a participant's epoch-level data (See section 3.1.3 Datasets for CGM DHT-Level Review).
SENSFL	Sensor First Record Flag	Char	Indicates the first epoch-level assessment timepoint associated with each new sensor session. The first epoch-level assessment

Variable Name	Variable Label	Type	Comments
			timepoint may correspond to the first record during a participant's warmup period where Analysis Value (AVAL) is null.
CRITy / CRITyFL / CRITyFN	Analysis Criterion y / Criterion y Evaluation Result Flag / Criterion y Evaluation Result Flag (N)	Char / Char / Num	CRITy identifies a pre-specified criterion within a parameter. CRITyFL and CRITyFN indicate whether the criterion is satisfied for the current record. Within the ADCGM dataset, it is encouraged that criteria variables be included in the ADCGM dataset when categorizations of the numeric CGM readings reported in AVAL are assessed based on the CGM-derived endpoints evaluated for the study. When relevant to the study, the criteria variables aid in traceability between the ADCGM dataset and the ADaM final analysis dataset. The definitions for the categorizations used within the study should be submitted within the study protocol and SAP with supporting literature as needed. See the example of these variables in Appendix 6.2. Note that if the identification of events such as level 1 or level 2 hypoglycemia or hyperglycemia episodes[16] includes duration that incorporates multiple CGM readings (e.g., a duration of at least 15 consecutive minutes where AVAL is <70 mg/dL to be categorized as level 1 hypoglycemia) separate analysis variables are recommended to be defined and used within the ADCGM dataset instead of the prespecified criteria variables. Note that the criteria variables are not appropriate in this scenario when multiple rows are being assessed to populate a single record.
ADTMCAy	Temporal Categorization y	Char	Categorization of Analysis Datetime (ADTM). It is recommended that ADTMCA1 represent the categorization of ADTM into daytime and nighttime for the individual epoch-level assessment timepoints. Subject to sponsor-defined controlled terminology (e.g., 'Diurnal', 'Nocturnal'). Rules to assign ADTMCA1 such as daily windows to indicate daytime and nighttime should be included within the SAP and study metadata (e.g., the ADRG and ADaM Define-XML file).
DCCGMDTM	Datetime of Discontinuation from CGM	Num	Datetime of the participant's discontinuation from the CGM DHT using an appropriate display format. May be originally reported within the Disposition (DS) dataset (See section 3.1.4 Disposition Dataset). DCCGMDTM is set to empty/null if a participant did not discontinue from the CGM DHT during the study.
AREASND	Analysis Reason Not Performed	Char	The primary reason why a CGM reading is missing for a given epoch, when known/collected. When LBREASND is populated, AREASND may not need to be derived in the ADCGM dataset. AREASND is only derived when needed; for example, AREASND may be useful to standardize the submitted values for reason using sponsor-defined terminology if not done so within the values for LBREASND. Similarly, if reason for missing epoch-level data is populated from other sources such as the SDTM DE dataset or from a participant diary reported in the Questionnaires (QS) dataset such

[16] Battelino T, Alexander CM, Amiel SA, Arreaza-Rubin G, Beck RW, Bergenstal RM, Buckingham BA, Carroll J, Ceriello A, Chow E, Choudhary P, Close K, Danne T, Dutta S, Gabbay R, Garg S, Heverly J, Hirsch IB, Kader T, Kenney J, Kovatchev B, Laffel L, Maahs D, Mathieu C, Mauricio D, Nimri R, Nishimura R, Scharf M, Del Prato S, Renard E, Rosenstock J, Saboo B, Ueki K, Umpierrez GE, Weinzimer SA, Phillip M., 2022, Continuous glucose monitoring and metrics for clinical trials: an international consensus statement., Lancet Diabetes Endocrinol., 11(1):42-57, doi: 10.1016/S2213-8587(22)00319-9.

Variable Name	Variable Label	Type	Comments
			that there are differences between LBREASND and AREASND, then AREASND is provided. The sponsor should provide details in the ADaM study metadata as to how AREASND is derived.
AREASCAy	Analysis Reason Category y	Char	Categorization of Analysis Reason Not Performed (AREASND) or LBREASND. It is recommended that AREASCA1 represents the binary categorization for reason as either 'participant-caused' or 'DHT-caused' for the missing CGM reading at the individual epoch-level assessment timepoint. The assignment of AREASCA1 is based on the analysis needs for the study. Additional categorizations may be added as needed for analysis. Rules used to assign AREASCA1 should be included within the SAP and study metadata (e.g., the ADRG and ADaM Define-XML file).
DTYPE	Derivation Type	Char	Populated as 'PHANTOM' to represent rows for missing epoch-level data that is not already present within the SDTM LB dataset.
Variables copied from input SDTM LB Dataset			
LBSEQ	Sequence Number	Num	Sponsors should include any SDTM variables in the ADCGM dataset needed to provide traceability to the source SDTM LB dataset. Specifically, LBDTC in ISO 8601 datetime format is requested to be provided within the ADCGM dataset.
LBDTC	Date/Time of Specimen Collection	Char	
LBSTAT	Completion Status	Char	Sponsors should include SDTM variables that provide explanations for missing CGM readings, when collected and reported by the CGM DHT. See Comments for LBSTAT and LBREASND provided in Table 1. Specifications for a Subset of LB Variables.
LBREASND	Reason Not Performed	Char	

To aid in epoch-level data analysis, additional epoch-level timing variables are recommended to be submitted. The sponsor should provide details on how time changes are handled within the epoch-level dataset (e.g., time change due to seasonality (i.e., due to daylight saving time and standard time shifts based on the participant's geographical location and the time of year) or change in time zone due to participant travel). An example of the additional epoch-level timing variables within the epoch-level dataset is shown in Appendix 6.2. Other data may be joined to the ADCGM dataset as needed for analysis and may be study specific. For example, to facilitate safety analyses, joining of insulin data from either the Exposure (EX) dataset or the Concomitant/Prior Medications (CM) dataset to the ADCGM dataset may be performed.

3.2.1.2 Windowing of Epoch-Level Assessment Timepoints

The analysis timing variable (e.g., AVISIT, ATPT, or other analysis timing variable) is a key variable within the ADaM ADCGM dataset that maps the individual epoch-level assessment timepoints to an analysis timing variable value (e.g., by day, week, or month) for analysis purposes depending on the CGM-derived endpoints used in the study. For example, the sponsor may implement a windowing strategy where the epoch-level data collected within the first two-week sensor session are attributed to AVISIT = 'Baseline', the epoch-level data collected within the second two-week sensor session are attributed to AVISIT = 'Week 2', etc. Details on the windowing of these individual epoch-level assessment timepoints to the appropriate analysis timing variable value are provided in the SAP. The algorithm used to assign values for the key

analysis timing variable is included in the software program(s) (source code) used to create the ADCGM dataset, and the algorithm details for the population of analysis timing variable value are provided in the ADaM Define-XML file.

To ensure the accuracy of the summarization of the epoch-level data within the final analysis datasets(s), the sponsor should confirm that the full timestamp (i.e., hours, minutes, seconds) is considered when assigning the analysis timing variable value so that the correct epoch-level data are included in the higher-level summaries. For example, an algorithm that only considers the date component when assigning values for AVISIT and does not consider the complete time component (00:00:00 through 23:59:59) may default to a single timestamp of midnight and erroneously not assign values for AVISIT for all epoch-level data that occur past midnight (i.e., from 00:00:01 through 23:59:59) on the same study day.

Epoch-level data in the ADCGM dataset with empty/null analysis timing variable values are excluded from the CGM summaries presented within the intermediate summary data and/or final analysis data. This can occur when extraneous epoch-level data are captured for a participant beyond the planned period of wear specified in the study protocol. These data do not have an analysis timing variable value populated based on the algorithm employed on the data and thus are considered 'outside' of the specified window for the analysis timing variable value. It is recommended that the reviewers' guide acknowledge the presence of these data and confirm that the corresponding analysis timing variable values for the affected CGM readings are not erroneously empty/null.

Applications should contain information explaining why CGM readings are collected outside of the specified window(s). The sponsor may also consider summarizing the reasons directly within the reviewers' guide, if feasible. However, if the reason(s) differ by participant and/or assessment timepoint, an additional record-level 'reason' variable in the ADCGM dataset explaining why the analysis timing variable value is empty/null for the affected CGM readings is recommended. The sponsor may consider using sponsor-defined terminology to standardize the submitted reason values. Additional windowing to assign the analysis timing variable value in the ADCGM dataset, including the sensitivity analysis performed, should be prespecified in the SAP. For example, if epoch-level data is planned to be captured during weeks 1-4 of the study but is actually captured during weeks 3-6, the CGM readings for weeks 5 and 6 will have the analysis timing variable value set to empty/null and no epoch-level data will be reported in the LB dataset for weeks 1 and 2. When the analysis timing variable value is empty/null the CGM readings for weeks 5 and 6 are considered to be outside of the window and are excluded from higher-level summaries. Providing the reason why a participant started their first sensor session two weeks later than planned and was not adherent to the defined schedule is useful for assessing and understanding excluded data.

3.2.1.3 Handling of Missing ADaM Epoch-Level Data

As discussed in SDTM section 3.1.1.2 Handling of Missing SDTM Epoch-Level Data, understanding the reasons for and prevalence of missing epoch-level data are critical to support FDA review and regulatory decision-making. Of importance to FDA is the standardized reporting of missing epoch-level data to evaluate systematic missingness and identify non-missing data trends and patterns. In the ADCGM dataset, sponsors should provide missing epoch-level data presented in the SDTM LB dataset with LB.LBSTAT = 'NOT DONE' and LB.LBREASND populated with a human-readable description of an error code or other output generated by the CGM DHT (see scenarios presented within Table 2. Recommended LB Representation of Missing CGM Epoch-Level Data). Though SDTM epoch-level data presented in the LB dataset may be limited to the data collected by the CGM DHT, the ADaM datasets maintain flexibility to include rows for missing data not originally provided in the SDTM. Thus, intermittent missing epoch-level data that were not originally included within the SDTM LB dataset (e.g., missing epoch-level data due to nonwear of the CGM DHT) should be added to the ADCGM dataset with Derivation Type (DTYPE) set to 'PHANTOM' for the affected rows.

Records for missing epoch-level data should be included in the ADCGM dataset for a participant's entire planned period of CGM wear during the study, unless the participant discontinued from the CGM DHT during the study. In this case, epoch-level data for missing data should be included in the ADCGM dataset up until the Datetime of Discontinuation from the CGM DHT (See the Datetime of Discontinuation from CGM (DCCGMDTM) variable in Table 3. Specifications for a Subset of ADCGM Variables). Rows for missing data after discontinuation are not provided in the ADCGM dataset.

It is recommended that the primary reason for the missing data be provided in the ADCGM dataset within Reason Not Performed (LBREASND), and if derived, the Analysis Reason Not Performed (AREASND) variable. As presented under AREASND within Table 3. Specifications for a Subset of ADBP Variables, the study metadata should clearly describe how the value of AREASND is assigned for the affected epoch-level data. AREASND is only derived when needed, such as when sponsor-defined terminology is used to standardize values for LBREASND or when an error code is transformed into a human-readable description. Reason for missing data may be provided from the CGM DHT (e.g., error codes), from the participant (e.g., from integrated subject diary data), or from another source (e.g., an event recorded in the SDTM DE dataset that describes a reason for missing data). When the reason is not collected, LBREASND and AREASND are empty/null.

For epoch-level data that are completely missing from the LB dataset due to nonwear or other reasons where epoch-level data is not collected and reported within the SDTM LB dataset, ideally the reason why the participant did not wear the CGM DHT is populated in the AREASND variable within the ADCGM dataset to aid in understanding the reasons for missing data. To capture this data, the sponsor may consider use of a participant diary in conjunction with the CGM DHT to capture compliance issues during the participant's planned period of wear. Data obtained via such a diary can enhance understanding of missing data, beyond the error codes that may be outputted directly by the CGM DHT. For example, an error code output by the

CGM DHT may acknowledge that early sensor termination occurred, but additional information provided by the participant can explain the cause of the early sensor termination event. Participant diary data may be represented in the SDTM Questionnaires (QS) dataset. It is recommended that the sponsor record the reason for missing data for participants during the study.

If the sponsor proposes imputing missing epoch-level data with non-null values in the ADCGM dataset, it is recommended that the sponsor consult with the Agency to determine whether the statistical methods proposed are appropriate to impute the missing epochs. To support this determination, the Agency may request validation or simulation studies from the sponsor for the proposed methods. When non-null epoch values are imputed within the Analysis Value (AVAL), Derivation Type (DTYPE) is populated with the imputation method used. When implemented, the sponsor should provide clear imputation rules with supporting rationale in the study SAP. Note that specific imputation methods are not specified in this document.

3.2.2 *ADaM Intermediate Summary Dataset*

As presented in section 1.2 Background the term *intermediate summary data* refers to the dataset(s) generated from the epoch-level dataset and bridges the epoch-level dataset and the final analysis dataset(s) used to evaluate CGM-derived endpoints. Intermediate summary data may not be necessary to be produced for CGM data when the ADaM epoch-level dataset (i.e., the ADCGM dataset) flows directly to the ADaM final analysis dataset(s). However, when created, intermediate summary dataset(s) are used to facilitate the creation of the final analysis dataset and should be submitted with other ADaM CGM datasets. For example, epoch-level data may first be summarized into an intermediate summary dataset showing CGM-derived endpoints by day, which may then be summarized in a final analysis dataset showing CGM-derived endpoints by the defined analysis timing variable (e.g., AVISIT). Other examples of possible intermediate datasets may involve summarization by week, by weekday vs. weekend, or by certain days of the week. Depending on the number of intermediate summaries produced, multiple intermediate datasets may be created and submitted.

3.2.3 *ADaM Final Analysis Dataset*

This section provides specifications for the ADaM dataset containing analysis-ready CGM data (referenced herein as the 'ADCGMEN' dataset), which are derived from the ADaM epoch-level ADCGM dataset as presented in section 3.2.1 ADaM Epoch-Level Dataset and/or the ADaM intermediate summary dataset (when created) as presented in section 3.2.2 ADaM Intermediate Summary Dataset, in conjunction with other ADaM data. Note that documentation of traceability from the ADCGMEN dataset to the preceding source dataset is needed; the study metadata, including the submitted software programs (source code), should be comprehensive such that the analysis measures prespecified in the SAP and provided within in the ADCGMEN dataset can be recreated by FDA.

3.2.3.1 General Considerations

The ADCGMEN dataset follows the ADaM BDS and contains the final analysis data used to evaluate CGM-derived endpoints and to produce the tables, listings, and figures for the CGM analyses presented within the Clinical Study Report (CSR). The summarization of the final analysis data by the analysis timing variable depends on the CGM-derived endpoints; for example, the ADCGMEN dataset may present parameters such as mean glucose concentration, glucose management indicator, glucose variability, and the percentage of time spent above, below, and/or within pre-defined glucose ranges. Table 4 contains specifications for a subset of ADCGMEN variables, some of which are standard ADaM BDS variables (included here to clarify how they should be completed for CGM data to foster consistency and standardization across industry as well as traceability) and some of which are newly defined. Table 4 does not include all variables that may be submitted within the ADCGMEN dataset. An example ADCGMEN dataset is provided in Appendix 6.3.

Table 4. Specifications for a Subset of ADCGMEN Variables

Variable Name	Variable Label	Type	Comments
AVISIT or ATPT	Analysis Visit or Analysis Timepoint	Char	The primary analysis timing variable (e.g., AVISIT, ATPT, or another analysis timing variable) used in the study to which the individual epoch-level assessment timepoints are mapped. Originally introduced within the ADCGM dataset (See section 3.2.1.2 Windowing of Epoch-Level Assessment Timepoints).
VALIDEPC	Valid Epochs	Num	The total number of CGM readings (i.e., valid epochs) from the epoch-level dataset used to compute a final analysis measure within the ADCGMEN dataset. The epochs included in VALIDEPC are limited to epoch-level records where ADCGM.AVAL is not empty/null (i.e., a CGM reading is provided within AVAL).
VALIDPTE	Valid Percentage Expected	Num	The expected percentage of valid epochs from the epoch-level dataset used to compute a final analysis measure within the ADCGMEN dataset to evaluate CGM DHT compliance. VALIDPTE is calculated using Valid Epochs (VALIDEPC) as the numerator and the total expected number of epoch-level records as the denominator, where the denominator may be calculated using the participant's planned start date and end date for the CGM DHT. For example, for a participant's one-week period of wear of a CGM DHT that collects data every 5 minutes, the denominator represents 7 days * 288 epoch-level records per day = 2,016 total expected number of records. The derivation of VALIDPTE should be clearly defined within the study metadata (See section 3.2.3.2 Handling of Missing ADaM Final Analysis Data).
CRITy / CRITyFL / CRITyFN	Analysis Criterion y / Criterion y Evaluation Result Flag / Criterion y Evaluation Result Flag (N)	Char / Char / Num	CRITy identifies a pre-specified criterion within a parameter. CRITyFL and CRITyFN indicate whether the criterion is satisfied for the current record. For CGM, it is recommended that criteria flags be used to indicate whether the Valid Percentage Expected (VALIDPTE) is less than a prespecified threshold for a participant. The threshold(s) used in the study should be defined within the SAP. An example of these variables is provided within Appendix 6.3.

3.2.3.2 Handling of Missing ADaM Final Analysis Data

Within the ADCGMEN dataset that encompasses the final analysis data, a row should be provided for each participant, parameter, and analysis timing variable (e.g., AVISIT or ATPT) where the final analysis measure is expected to be populated based on the participant's planned period of CGM DHT wear originally presented within the study protocol, unless the participant discontinued from the CGM DHT at an earlier point during the study. In this case, records for missing data should be included in the ADCGMEN dataset up until the Datetime of Discontinuation from the CGM DHT (See Datetime of Discontinuation from CGM (DCCGMDTM) in Table 4. Specifications for a Subset of ADCGMEN Variables). Note that in general, rows for missing CGM data after discontinuation from the CGM DHT are not expected to be provided in the ADCGMEN dataset.

Given the presence of phantom records in the ADCGM dataset to represent cases of intermittent missingness for a participant, there may be cases where AVAL is empty/null for a given final analysis measure in the ADCGMEN dataset due to missing CGM readings. For this scenario, a row is provided in the ADCGMEN dataset for the participant, parameter, and analysis timing variable. Alternate DTYPE values may be used to handle missing AVAL values and depend on the imputation methods implemented. When implemented, the sponsor should provide clear imputation rules with supporting rationale in the study SAP. Note that imputation methods are not specified within this document.

The data quality variables presented in Table 4. Specifications for a Subset of ADCGMEN Variables aid in traceability and an understanding of the amount of data that contributes toward the final analysis measures presented within the ADCGMEN dataset. An example of these variables is shown in the ADCGMEN dataset within Appendix 6.3. FDA is interested in the threshold for the percentage of valid records needed for a final analysis measure to be calculated and subsequently used in analysis (i.e., used to produce the tables, listings, and figures for the CGM analyses presented in the CSR). The selected threshold(s) and the corresponding rationale that comprises a 'complete' assessment should be clearly defined in the SAP. For example, a sponsor may indicate in the SAP that records used in analysis should have a valid percentage $\geq$ 70% over a 14-day period.[17] Sensitivity analyses to assess the impact of filtering on complete assessments when calculating the final analysis results should also be prespecified in the SAP. Tables requested by the Agency to analyze missing data are specified within section 4.0 Specifications for Tables and Figures.

[17] Battelino T, Alexander CM, Amiel SA, Arreaza-Rubin G, Beck RW, Bergenstal RM, Buckingham BA, Carroll J, Ceriello A, Chow E, Choudhary P, Close K, Danne T, Dutta S, Gabbay R, Garg S, Heverly J, Hirsch IB, Kader T, Kenney J, Kovatchev B, Laffel L, Maahs D, Mathieu C, Mauricio D, Nimri R, Nishimura R, Scharf M, Del Prato S, Renard E, Rosenstock J, Saboo B, Ueki K, Umpierrez GE, Weinzimer SA, Phillip M., 2022, Continuous glucose monitoring and metrics for clinical trials: an international consensus statement., Lancet Diabetes Endocrinol., 11(1):42-57, doi: 10.1016/S2213-8587(22)00319-9.

3.2.4 *ADaM Paired Glucose Analysis Dataset*

This section describes an additional ADaM dataset used to generate a paired glucose analysis (herein referenced as the 'ADGLUCPR' dataset) that joins CGM epoch-level data and non-CGM glucose data. Of interest to FDA is the clarity in which epoch-level data captured by a CGM DHT can be assessed against non-CGM-derived glucose data in clinical investigations where the protocol specifies that non-CGM glucose data be collected concurrently with CGM epoch-level data. Relevant non-CGM glucose data may be collected remotely by the participant (e.g. glucose data collected with a glucometer or fingerstick) or on site by a venous blood draw at specified visits. Non-CGM glucose data are presented in the SDTM LB dataset and the ADaM dataset that summarize other laboratory results (referenced in this section as the 'ADLB').

Joined CGM and non-CGM glucose data can complement reported CGM readings when the values of CGM and non-CGM data that are collected in a similar time window are aligned. To increase the effectiveness of the evaluation of CGM epoch-level data, a standalone ADaM ADGLUCPR dataset may be submitted. The sponsor may consult with the Agency to confirm whether the ADGLUCPR dataset is recommended as part of the CGM data submission for a given study.

Non-CGM-derived glucose data may be specified in the protocol to be collected for calibration of the CGM DHT, for confirmation of a hyper- or hypoglycemic event based on an alert received, or for other reasons. When calibration of the CGM DHT is required, the participant may be able to manually input the non-CGM glucose reading into the CGM receiver. Similarly, when capturing non-CGM glucose data to assess predictive alert performance (i.e., to confirm a hyper- or hypoglycemic event), a participant may use non-CGM glucose data to confirm the accuracy of the CGM alert and to check whether the non-CGM glucose reading is in agreement with the generally accepted range of CGM readings collected over a certain time range. For example, if CGM is used to capture level 2 hypoglycemia and alerts the participant to CGM values less than 54 mg/dL, a participant may collect a confirmatory non-CGM glucose reading after an alert.

The ADGLUCPR dataset presents CGM epoch-level data alongside non-CGM glucose data. The ADGLUCPR dataset may not fit within the ADaM BDS and is instead classified as ADaM OTHER. Unlike the ADCGM dataset shown in section 3.2.1 ADaM Epoch-Level Dataset that presents all epoch-level data, only the subset of epoch-level data that have a paired non-CGM glucose reading are included within the ADGLUCPR dataset. To identify paired glucose readings, it is recommended that the sponsor define a window for CGM readings in the SAP. For example, a timeframe of 5 to 30 minutes may be defined to assess how multiple CGM readings compare to a single non-CGM glucose reading. A larger window will increase the probability that at least one CGM reading can be identified within the window to compare against a corresponding non-CGM glucose reading. Assessing multiple CGM readings that occur within the defined window will illustrate how data is trending across multiple epoch-level assessment timepoints instead of viewing a single CGM reading at a point-in-time. To support traceability, the sponsor should submit the software program (source code) used to create the ADGLUCPR

dataset, including the algorithm employed to pair the CGM epoch-level data and non-CGM glucose data.

Table 5 contains specifications for the newly defined variables to be submitted within the ADGLUCPR dataset but does not include all variables to be submitted within an ADaM dataset. For example, variables from the ADaM ADSL dataset that enable demographic subgroup analysis (e.g., age, sex, race, ethnicity), variables that are used for stratification, and other covariates needed for analysis should also be provided within the ADGLUCPR dataset. An example ADGLUCPR dataset is provided in Appendix 6.4.

Table 5. Specifications for ADGLUCPR Variables

Variable Name	Variable Label	Type	Comments
NCGMPARM	Non-CGM Parameter	Char	The description of the non-CGM parameter that includes all descriptive and qualifying information such as units needed to interpret the numeric analysis value reported in NCGMVAL.
NCGMVAL	Non-CGM Value	Num	Numeric analysis value of the paired non-CGM glucose reading reported within ADLB.AVAL.
NCGMCAy / NCGMCAyN	Non-CGM Value Category y / Non-CGM Value Category y (N)	Char / Num	Categorization variables used to categorize the non-CGM glucose readings reported within NCGMVAL. The sponsor may use the same categories defined for the study as reported within the ADCGM dataset presented in Table 3. Specifications for a Subset of ADCGM Variables.
NCGMDTM	Non-CGM Analysis Datetime	Num	Datetime of the non-CGM glucose readings reported within ADLB.ADTM using an appropriate display format.
NCGMID	Non-CGM Identifier	Char	Unique identifier for a non-CGM glucose value reported in NCGMVAL at a distinct timepoint. NCGMID may be derived or, to support datapoint traceability, may be populated based on a unique identifier variable within the LB or ADLB dataset (e.g., LBSEQ, LBSPID).
CGMPARM	CGM Parameter	Char	The description of the CGM parameter that includes all descriptive and qualifying information such as units needed to interpret the numeric analysis value reported in CGMVAL.
CGMVAL	CGM Value	Num	Numeric analysis value of the paired CGM glucose reading reported within ADCGM.AVAL.
CGMCAy / CGMCAyN	CGM Value Category y / CGM Value Category y (N)	Char / Num	Categorization variables used to categorize the CGM readings reported within CGMAVAL. The sponsor may use the same categories reported within the ADCGM dataset presented in Table 3. Specifications for a Subset of ADCGM Variables.
CGMDTM	CGM Datetime	Num	Datetime of individual epoch-level assessment timepoints using an appropriate display format.
CGMID	CGM Identifier	Char	Unique identifier for a CGM glucose value reported in CGMVAL at a distinct epoch-level timepoint. CGMID may be derived or, to support datapoint traceability, may be populated based on a unique identifier variable within the ADCGM dataset.
ABSDIFF	Absolute Difference	Num	Absolute difference of the CGM reading reported in CGMVAL and the non-CGM glucose reading reported in NCGMVAL.
PCTDIFF	Percent Difference	Num	Percent difference calculated using the Absolute Difference (ABSDIFF) as the numerator and the non-CGM glucose reading reported in NCGMVAL as the denominator.

Variable Name	Variable Label	Type	Comments
DTMDIFF	Datetime Difference	Char	Difference in datetime reported in minutes between the non-CGM datetime reported in NCGMDTM and the CGM datetime reported in CGMDTM. Reported in ISO 8601 duration format.
CDTMFL	Closest Time Identifier Flag	Char	Indicates the closest datetime as 'Y' based on the non-CGM datetime reported in NCGMDTM and the CGM datetime reported in CGMDTM. Relevant when CGM readings across multiple epochs map to a single non-CGM glucose reading based on the defined window. If the closest datetime affects multiple paired glucose records (i.e., the CGM value taken before the non-CGM value is equidistant to the CGM value taken after the non-CGM value), then CDTMFL is flagged as 'Y' for each record.
CVALFL	Closest Value Identifier Flag	Char	Indicates the closest value(s) as 'Y' of the non-CGM reading reported in NCGMVAL and the CGM reading reported in CGMVAL. Relevant when CGM readings across multiple epochs map to a single non-CGM glucose reading and based on the smallest ABSDIFF value(s). If the closest value affects multiple paired glucose records, then CVALFL is flagged as 'Y' for each record.

4.0 SPECIFICATIONS FOR TABLES AND FIGURES

In addition to the sponsor's prespecified tables and figures presenting analyses for CGM-derived endpoints, the Agency recommends that the following be provided within the CSR to facilitate the evaluation of the CGM data.

- A data completeness summary table to represent the proportion of complete data for each treatment arm and unit of time (e.g., day, week, month) for subjects who did not discontinue CGM DHT during the study. Though multiple summaries may be created to represent different units of time, it is recommended that a table be created to summarize data by the primary analysis timing variable (e.g., AVISIT, ATPT, or another analysis timing variable). An example table is provided in Appendix 6.5.

- A missing data summary table to represent the proportion of missing data for each treatment arm and reason for missing data. An example table is provided in Appendix 6.5.

- Paired CGM and non-CGM visualization(s) to aid in the evaluation of paired glucose data within the ADGLUCPR dataset when relevant to the study. For example, a visualization to compare glucose categorizations (i.e., CGMCAy and NCGMCAy as presented in Table 5. Specifications for ADGLUCPR Variables) may be useful.

The sponsor may consult with the Agency for further clarity on the analyses to be submitted.

5.0 REFERENCES

Battelino, T, CM Alexander, SA Amiel, G Arreaza-Rubin, RW Beck, RM Bergenstal, BA Buckingham, J Carroll, A Ceriello, E Chow, P Choudhary, K Close, T Danne, S Dutta, R Gabbay, S Garg, J Heverly, IB Hirsch, T Kader, J Kenney, B Kovatchev, L Laffel, D Maahs, C Mathieu, D Mauricio, R Nimri, R Nishimura, M Scharf, S Del Prato, E Renard, J Rosenstock, B Saboo, K Ueki, GE Umpierrez, SA Weinzimer, and M Phillip, 2022, Continuous glucose monitoring and metrics for clinical trials: an international consensus statement., Lancet Diabetes Endocrinol., 11(1):42-57.

6.0 APPENDIX

The example datasets in sections 6.1-6.4 below represent continuous glucose monitoring (CGM) datasets for steps of the CGM data flow for Study A, including the SDTM epoch-level dataset, the ADaM epoch-level dataset, and the ADaM final analysis dataset used to evaluate CGM-derived endpoints. In addition, a separate dataset is provided to summarize paired glucose data. In these examples, the epoch length of the CGM DHT is five minutes, resulting in CGM readings reported every five minutes within the SDTM LB dataset and the ADaM ADCGM dataset. Based on the example study protocol (not pictured), CGM is worn by participants in the clinical trial over a period of three months and the sensor is replaced every seven days.

In this example, ADaM epoch-level data is submitted within the ADCGM dataset. Thus, the additional epoch-level timing variables are created as analysis variables within the ADCGM dataset and are shown in Table A2. Alternatively, additional epoch-level timing variables may be submitted in SDTM as non-standard variables within the SUPPLB dataset if an ADaM epoch-level dataset is not created for a study. The ADaM final analysis dataset (i.e., the ADCGMEN dataset) contains the CGM-derived endpoints. Within example Table A3, a single endpoint for time in range is shown. Per the study protocol (not pictured), at least 70% of epoch-level data should be valid observations (i.e., AVAL is not empty/null) to compute the CGM-derived endpoint for each subject and analysis visit within the ADCGMEN dataset.

Note that the datasets below do not include all variables to be submitted within the SDTM and ADaM datasets, and the numeric CGM readings and other values within AVAL are provided for illustrative purposes only. In addition to the dataset examples, section 6.5 shows example tables and figures.

6.1 Example SDTM Laboratory Test Results Dataset (LB Dataset)

Table A1 reports epoch-level data captured by the CGM DHT for a subset of CGM records for a single subject in the LB dataset. CGM readings are collected every five minutes as reflected by the frequency of datetime value shown in LBDTC. Because the subset of data shown in Table A1 is limited to CGM epoch-level data, LBMETHOD = ‘CGM’ is not shown in the example but is the same for all records in the subset. Scenarios displayed in Table A1 include:

- The patient began their second sensor session on January 8, 2024, at 8 AM on day 1 of the study. The first sensor session, starting on LBDY = -7, comprised the weeklong baseline period and is not shown in the subset. As noted in the study protocol (not pictured), the warmup period for the CGM DHT at the start of each new sensor session has a duration of approximately two hours. Thus, epoch-level data records from 8 AM to 9:55 AM (i.e., rows 1 through 24 in Table A1) do not have numeric CGM readings (i.e., LBORRES is empty/null).
    - For the CGM DHT used in Study A, individual epoch-level records to indicate the warmup period were collected and transmitted, and thus were submitted within the LB dataset. For these records, LBSTAT = ‘NOT DONE’ and LBREASND = ‘WARMUP PERIOD’.

  - The first CGM reading is reported in Row 25 after the two-hour warmup period concludes. CGM readings are reported for each epoch until the morning of day 8, ending with Row 2022.

- The patient replaced the sensor and began their third sensor session on January 15, 2024, at 8 AM (day 8 of the study) as shown in Row 2023. Similar to the second sensor session, the patient underwent a two-hour warmup period. Epoch-level data for the affected records show LBSTAT = 'NOT DONE' and LBREASND = 'WARMUP PERIOD'.

  - The first CGM reading for the third sensor session is reported in Row 2047. CGM readings are reported for each epoch until day 11 of the study when an unanticipated event occurred for the CGM DHT.

- On day 11 of the study, January 18, 2024, at 12:15 PM, an early sensor termination event occurred as shown in Row 2941. According to a subject diary populated by the subject throughout the study (not pictured), the sensor was partially removed accidentally, which was initially unknown to the subject for several hours.

  - Between 12:15 PM and 3 PM on day 11 of the study (i.e., rows 2941 – 2974), the CGM DHT consistently outputted an error code that indicated the sensor was not active. These rows are present in the LB dataset for the affected epoch-level data since the error codes are collected by the CGM DHT during the study, where LBSTAT = 'NOT DONE' and LBREASND = 'SENSOR NOT ACTIVE'.

- Around 3:12 PM on day 11 of the study, the subject replaced the sensor and commenced the fourth sensor session. In Row 2975, the first epoch-level data row for the fourth sensor session is reported. The subject underwent the two-hour warmup period starting at 3:12 PM where the affected records show LBSTAT = 'NOT DONE' and LBREASND = 'WARMUP PERIOD'.

- CGM readings are reported for the fourth sensor session until the morning of day 18 shown on Row 4912. At this time, the patient is supposed to immediately replace their sensor per the study protocol, but the sensor was not replaced for several hours. Thus, the next epoch-level data row is not reported until 4:35 PM when the fifth sensor session starts, commencing with the warmup period as shown in Row 4913. Since no data was collected by the CGM DHT between 8:38 AM and 4:34 PM, there are no rows reported in the SDTM LB dataset. Instead, rows for missing data are added in the ADaM ADCGM dataset as shown in Table A2.

Note that in Table A1 color coding is used to separate the four sensor sessions illustrated within the table to aid in interpretation and ease of understanding.

Table A1. SDTM Epoch-Level Dataset Example

Row	USUBJID	LBTEST	LBORRES	LBORRESU	LBSTAT	LBREASND	LBDTC	LBDY
1	A_100_1	Glucose			NOT DONE	WARMUP PERIOD	2024-01-08T08:00:00	1
2	A_100_1	Glucose			NOT DONE	WARMUP PERIOD	2024-01-08T08:05:00	1
3	A_100_1	Glucose			NOT DONE	WARMUP PERIOD	2024-01-08T08:10:00	1
…						…		
23	A_100_1	Glucose			NOT DONE	WARMUP PERIOD	2024-01-08T09:50:00	1
24	A_100_1	Glucose			NOT DONE	WARMUP PERIOD	2024-01-08T09:55:00	1
25	A_100_1	Glucose	165	mg/dL			2024-01-08T10:00:00	1
26	A_100_1	Glucose	162	mg/dL			2024-01-08T10:05:00	1
27	A_100_1	Glucose	167	mg/dL			2024-01-08T10:10:00	1
28	A_100_1	Glucose	172	mg/dL			2024-01-08T10:15:00	1
29	A_100_1	Glucose	176	mg/dL			2024-01-08T10:20:00	1
…								
49	A_100_1	Glucose	179	mg/dL			2024-01-08T12:00:00	1
50	A_100_1	Glucose	181	mg/dL			2024-01-08T12:05:00	1
51	A_100_1	Glucose	194	mg/dL			2024-01-08T12:10:00	1
52	A_100_1	Glucose	187	mg/dL			2024-01-08T12:15:00	1
…								
66	A_100_1	Glucose	183	mg/dL			2024-01-08T13:25:00	1
67	A_100_1	Glucose	175	mg/dL			2024-01-08T13:30:00	1
68	A_100_1	Glucose	172	mg/dL			2024-01-08T13:35:00	1
…								
2022	A_100_1	Glucose	143	mg/dL			2024-01-15T07:55:00	8
2023	A_100_1	Glucose			NOT DONE	WARMUP PERIOD	2024-01-15T08:00:00	8
2024	A_100_1	Glucose			NOT DONE	WARMUP PERIOD	2024-01-15T08:05:00	8
2025	A_100_1	Glucose			NOT DONE	WARMUP PERIOD	2024-01-15T08:10:00	8
…								
2045	A_100_1	Glucose			NOT DONE	WARMUP PERIOD	2024-01-15T09:50:00	8

Row	USUBJID	LBTEST	LBORRES	LBORRESU	LBSTAT	LBREASND	LBDTC	LBDY
2046	A_100_1	Glucose			NOT DONE	WARMUP PERIOD	2024-01-15T09:55:00	8
2047	A_100_1	Glucose	140	mg/dL			2024-01-15T10:00:00	8
2048	A_100_1	Glucose	147	mg/dL			2024-01-15T10:05:00	8
2049	A_100_1	Glucose	139	mg/dL			2024-01-15T10:10:00	8
…								
2938	A_100_1	Glucose	126	mg/dL			2024-01-18T12:00:00	11
2939	A_100_1	Glucose	123	mg/dL			2024-01-18T12:05:00	11
2940	A_100_1	Glucose	114	mg/dL			2024-01-18T12:10:00	11
2941	A_100_1	Glucose			NOT DONE	SENSOR NOT ACTIVE	2024-01-18T12:15:00	11
2942	A_100_1	Glucose			NOT DONE	SENSOR NOT ACTIVE	2024-01-18T12:20:00	11
…								
2974	A_100_1	Glucose			NOT DONE	SENSOR NOT ACTIVE	2024-01-18T15:00:00	11
2975	A_100_1	Glucose			NOT DONE	WARMUP PERIOD	2024-01-18T15:12:00	11
2976	A_100_1	Glucose			NOT DONE	WARMUP PERIOD	2024-01-18T15:17:00	11
2977	A_100_1	Glucose			NOT DONE	WARMUP PERIOD	2024-01-18T15:22:00	11
…								
4808	A_100_1	Glucose	97	mg/dL			2024-01-24T23:57:00	17
4809	A_100_1	Glucose	88	mg/dL			2024-01-25T00:02:00	18
4810	A_100_1	Glucose	81	mg/dL			2024-01-25T00:07:00	18
…								
4912	A_100_1	Glucose	94	mg/dL			2024-01-25T08:37:00	18
4913	A_100_1	Glucose			NOT DONE	WARMUP PERIOD	2024-01-25T16:35:00	18
4914	A_100_1	Glucose			NOT DONE	WARMUP PERIOD	2024-01-25T16:40:00	18

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6.2 Example ADaM CGM Epoch-Level Dataset (ADCGM Dataset)

Table A2, shown in three parts, shows the ADaM ADCGM epoch-level dataset submitted as a basic data structure (BDS) for a single subject. Note that the scenarios displayed in Table A2 align with the scenarios initially described in the SDTM epoch-level data shown in Table A1. The ordering of variables within the table is incidental to group similar variables for illustrative purposes and is not part of the specification for the ADCGM dataset.

Within Table A2, Analysis Visit (AVISIT) is the key timing variable used for analysis in Study A. AVISIT is populated for rows in the ADCGM dataset by assigning consecutive epochs to a single AVISIT value according to the windowing schedule outlined within the statistical analysis plan (SAP) (not shown). Variables from the SDTM epoch-level dataset (e.g., LBDTC, LBSTAT, and LBREASND) are populated within the ADCGM dataset to support traceability. Note that since the participant in the example did not discontinue CGM use, the Datetime of Discontinuation from CGM (DCCGMDTM) is not shown within the subset. Additional variables used to support analysis include the following:

Timing variables:

- Analysis Visit (AVISIT) is assigned by week (e.g., 'Week 1', 'Week 2') based on the Analysis Relative Day (ADY) according to the Study A protocol (not pictured)

- Temporal Categorization 1 (ADTMCA1) categorizes epoch-level data as either 'DIURNAL' or 'NOCTURNAL' based on the windows used to indicate daytime and nighttime within the study SAP (not pictured)

- The additional epoch-level timing variables are presented in Part 3 of Table A2 and include Analysis Duration Elapsed from Midnight (AELPDUR), Analysis Elapsed Day (AELPDY), Analysis Day of Week (ADYWK), Analysis Adjusted Date/Time (AADJDTC), Analysis Hour (AHR), and Analysis Minute (AMN)

Sensor-level variables:

- Per the ADaM Define-XML file (not shown), Sponsor Device Identifier (SPDEVID) is used to identify each sensor. SPDEVID is populated for the collected epoch-level data to differentiate CGM readings by sensor. Epoch-level data with identical SPDEVID values are associated with the same CGM sensor session.

- Sensor First Record Flag (SENSFL) is populated as 'Y' to indicate the first epoch associated with each new sensor session as shown in rows 1, 2023, 2975, and 5008.

Categorization variables:

- Criteria variables are included to aid in the interpretation and categorization of CGM readings reported within AVAL. Within Table A2, CRIT1 and CRIT1FL are included to indicate hyperglycemia for individual CGM readings. Per the study protocol (not shown), a

CGM reading is labeled hyperglycemic if it exceeds 180 mg/dL as shown in rows 50-66, where CRIT1 = 'Hyperglycemia (AVAL > 180)' and CRIT1FL = 'Y' for the affected records. Note that only the criteria variables relevant to the subset of CGM readings shown in Table A2 are included in the example. Other criteria may be defined as needed within a study based on the CGM-derived endpoints.

Variables to support missing data:

- Derivation Type (DTYPE) is populated with 'PHANTOM' to represent rows for intermittent missingness for epoch-level data that are missing from the LB dataset which affects rows 4913-5007.

- Analysis Reason Not Performed (AREASND) is populated with the reason that the CGM reading is missing. For records where LBREASND is populated in the LB dataset, LBREASND = AREASND. For the affected phantom records in rows 4913-5007, the value of 'PARTICIPANT FORGOT' is populated based on participant diary data (not shown) because the participant did not replace their sensor immediately after removing the old sensor as specified in the protocol.

    - Analysis Reason Category 1 (AREASCA1) categorizes reason as either 'DHT-CAUSED' or 'PARTICIPANT-CAUSED'.

Table A2. (Part 1) ADCGM Dataset Example

Row	USUBJID	PARAM	AVAL	AVISIT	ADTM	LBDTC	ADY	SENSFL
1	A_100_1	Glucose (mg/dL)		Week 1	08Jan2024 8:00:00 AM	2024-01-08T08:00:00	1	Y
2	A_100_1	Glucose (mg/dL)		Week 1	08Jan2024 8:05:00 AM	2024-01-08T08:05:00	1	
3	A_100_1	Glucose (mg/dL)		Week 1	08Jan2024 8:10:00 AM	2024-01-08T08:10:00	1	
…								
23	A_100_1	Glucose (mg/dL)		Week 1	08Jan2024 9:50:00 AM	2024-01-08T09:50:00	1	
24	A_100_1	Glucose (mg/dL)		Week 1	08Jan2024 9:55:00 AM	2024-01-08T09:55:00	1	
25	A_100_1	Glucose (mg/dL)	165	Week 1	08Jan2024 10:00:00 AM	2024-01-08T10:00:00	1	
26	A_100_1	Glucose (mg/dL)	162	Week 1	08Jan2024 10:05:00 AM	2024-01-08T10:05:00	1	
27	A_100_1	Glucose (mg/dL)	167	Week 1	08Jan2024 10:10:00 AM	2024-01-08T10:10:00	1	
28	A_100_1	Glucose (mg/dL)	172	Week 1	08Jan2024 10:15:00 AM	2024-01-08T10:15:00	1	
29	A_100_1	Glucose (mg/dL)	176	Week 1	08Jan2024 10:20:00 AM	2024-01-08T10:20:00	1	
…								
49	A_100_1	Glucose (mg/dL)	179	Week 1	08Jan2024 12:00:00 PM	2024-01-08T12:00:00	1	
50	A_100_1	Glucose (mg/dL)	181	Week 1	08Jan2024 12:05:00 PM	2024-01-08T12:05:00	1	
51	A_100_1	Glucose (mg/dL)	194	Week 1	08Jan2024 12:10:00 PM	2024-01-08T12:10:00	1	
52	A_100_1	Glucose (mg/dL)	187	Week 1	08Jan2024 12:15:00 PM	2024-01-08T12:15:00	1	
…								
66	A_100_1	Glucose (mg/dL)	183	Week 1	08Jan2024 1:25:00 PM	2024-01-08T13:25:00	1	
67	A_100_1	Glucose (mg/dL)	175	Week 1	08Jan2024 1:30:00 PM	2024-01-08T13:30:00	1	
68	A_100_1	Glucose (mg/dL)	172	Week 1	08Jan2024 1:35:00 PM	2024-01-08T13:35:00	1	
…								
2022	A_100_1	Glucose (mg/dL)	143	Week 2	15Jan2024 7:55:00 AM	2024-01-15T07:55:00	8	
2023	A_100_1	Glucose (mg/dL)		Week 2	15Jan2024 8:00:00 AM	2024-01-15T08:00:00	8	Y
2024	A_100_1	Glucose (mg/dL)		Week 2	15Jan2024 8:05:00 AM	2024-01-15T08:05:00	8	
2025	A_100_1	Glucose (mg/dL)		Week 2	15Jan2024 8:10:00 AM	2024-01-15T08:10:00	8	
…								
2045	A_100_1	Glucose (mg/dL)		Week 2	15Jan2024 9:50:00 AM	2024-01-15T09:50:00	8	
2046	A_100_1	Glucose (mg/dL)		Week 2	15Jan2024 9:55:00 AM	2024-01-15T09:55:00	8	
2047	A_100_1	Glucose (mg/dL)	140	Week 2	15Jan2024 10:00:00 AM	2024-01-15T10:00:00	8	
2048	A_100_1	Glucose (mg/dL)	147	Week 2	15Jan2024 10:05:00 AM	2024-01-15T10:05:00	8	

Row	USUBJID	PARAM	AVAL	AVISIT	ADTM	LBDTC	ADY	SENSFL
2049	A_100_1	Glucose (mg/dL)	139	Week 2	15Jan2024 10:10:00 AM	2024-01-15T10:10:00	8	
…								
2938	A_100_1	Glucose (mg/dL)	126	Week 2	18Jan2024 12:00:00 PM	2024-01-18T12:00:00	11	
2939	A_100_1	Glucose (mg/dL)	123	Week 2	18Jan2024 12:05:00 PM	2024-01-18T12:05:00	11	
2940	A_100_1	Glucose (mg/dL)	114	Week 2	18Jan2024 12:10:00 PM	2024-01-18T12:10:00	11	
2941	A_100_1	Glucose (mg/dL)		Week 2	18Jan2024 12:15:00 PM	2024-01-18T12:15:00	11	
2942	A_100_1	Glucose (mg/dL)		Week 2	18Jan2024 12:20:00 PM	2024-01-18T12:20:00	11	
…								
2974	A_100_1	Glucose (mg/dL)		Week 2	18Jan2024 3:00:00 PM	2024-01-18T15:00:00	11	
2975	A_100_1	Glucose (mg/dL)		Week 2	18Jan2024 3:12:00 PM	2024-01-18T15:12:00	11	Y
2976	A_100_1	Glucose (mg/dL)		Week 2	18Jan2024 3:17:00 PM	2024-01-18T15:17:00	11	
2977	A_100_1	Glucose (mg/dL)		Week 2	18Jan2024 3:22:00 PM	2024-01-18T15:22:00	11	
…								
4808	A_100_1	Glucose (mg/dL)	97	Week 3	24Jan2024 11:57:00 PM	2024-01-24T23:57:00	17	
4809	A_100_1	Glucose (mg/dL)	88	Week 3	25Jan2024 12:02:00 AM	2024-01-25T00:02:00	18	
4810	A_100_1	Glucose (mg/dL)	81	Week 3	25Jan2024 12:07:00 AM	2024-01-25T00:07:00	18	
…								
4912	A_100_1	Glucose (mg/dL)	94	Week 3	25Jan2024 8:37:00 AM	2024-01-25T08:37:00	18	
4913	A_100_1	Glucose (mg/dL)		Week 3	25Jan2024 8:42:00 AM		18	
4914	A_100_1	Glucose (mg/dL)		Week 3	25Jan2024 8:47:00 AM		18	
4915	A_100_1	Glucose (mg/dL)		Week 3	25Jan2024 8:52:00 AM		18	
4916	A_100_1	Glucose (mg/dL)		Week 3	25Jan2024 8:57:00 AM		18	
…								
5007	A_100_1	Glucose (mg/dL)		Week 3	25Jan2024 4:32:00 PM		18	
5008	A_100_1	Glucose (mg/dL)		Week 3	25Jan2024 4:35:00 PM	2024-01-25T16:35:00	18	Y
5009	A_100_1	Glucose (mg/dL)		Week 3	25Jan2024 4:40:00 PM	2024-01-25T16:40:00	18	

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Table A2. (Part 2) ADCGM Dataset Example

Row	SPDEVID	CRIT1	CRIT1FL	LBSTAT	LBREASND	ADTMCA1	AREASCA1
1	(01)1234567890123(21)S123(10)1.0			NOT DONE	WARMUP PERIOD	DIURNAL	DHT-CAUSED
2	(01)1234567890123(21)S123(10)1.0			NOT DONE	WARMUP PERIOD	DIURNAL	DHT-CAUSED
3	(01)1234567890123(21)S123(10)1.0			NOT DONE	WARMUP PERIOD	DIURNAL	DHT-CAUSED
…					…		
23	(01)1234567890123(21)S123(10)1.0			NOT DONE	WARMUP PERIOD	DIURNAL	DHT-CAUSED
24	(01)1234567890123(21)S123(10)1.0			NOT DONE	WARMUP PERIOD	DIURNAL	DHT-CAUSED
25	(01)1234567890123(21)S123(10)1.0					DIURNAL	
26	(01)1234567890123(21)S123(10)1.0					DIURNAL	
27	(01)1234567890123(21)S123(10)1.0					DIURNAL	
28	(01)1234567890123(21)S123(10)1.0					DIURNAL	
29	(01)1234567890123(21)S123(10)1.0					DIURNAL	
…							
49	(01)1234567890123(21)S123(10)1.0					DIURNAL	
50	(01)1234567890123(21)S123(10)1.0	Hyperglycemia (AVAL > 180)	Y			DIURNAL	
51	(01)1234567890123(21)S123(10)1.0	Hyperglycemia (AVAL > 180)	Y			DIURNAL	
52	(01)1234567890123(21)S123(10)1.0	Hyperglycemia (AVAL > 180)	Y			DIURNAL	
…						DIURNAL	
66	(01)1234567890123(21)S123(10)1.0	Hyperglycemia (AVAL > 180)	Y			DIURNAL	
67	(01)1234567890123(21)S123(10)1.0					DIURNAL	
68	(01)1234567890123(21)S123(10)1.0					DIURNAL	
…							

Row	SPDEVID	CRIT1	CRIT1FL	LBSTAT	LBREASND	ADTMCA1	AREASCA1
2022	(01)1234567890123(21)S123(10)1.0					DIURNAL	
2023	(01)1234567890123(21)S123(10)2.0			NOT DONE	WARMUP PERIOD	DIURNAL	DHT-CAUSED
2024	(01)1234567890123(21)S123(10)2.0			NOT DONE	WARMUP PERIOD	DIURNAL	DHT-CAUSED
2025	(01)1234567890123(21)S123(10)2.0			NOT DONE	WARMUP PERIOD	DIURNAL	DHT-CAUSED
…						DIURNAL	
2045	(01)1234567890123(21)S123(10)2.0			NOT DONE	WARMUP PERIOD	DIURNAL	DHT-CAUSED
2046	(01)1234567890123(21)S123(10)2.0			NOT DONE	WARMUP PERIOD	DIURNAL	DHT-CAUSED
2047	(01)1234567890123(21)S123(10)2.0					DIURNAL	
2048	(01)1234567890123(21)S123(10)2.0					DIURNAL	
2049	(01)1234567890123(21)S123(10)2.0					DIURNAL	
…						DIURNAL	
2938	(01)1234567890123(21)S123(10)2.0					DIURNAL	
2939	(01)1234567890123(21)S123(10)2.0					DIURNAL	
2940	(01)1234567890123(21)S123(10)2.0					DIURNAL	
2941	(01)1234567890123(21)S123(10)2.0			NOT DONE	SENSOR NOT ACTIVE	DIURNAL	DHT-CAUSED
2942	(01)1234567890123(21)S123(10)2.0			NOT DONE	SENSOR NOT ACTIVE	DIURNAL	DHT-CAUSED
…							
2974	(01)1234567890123(21)S123(10)2.0			NOT DONE	SENSOR NOT ACTIVE	DIURNAL	DHT-CAUSED
2975	(01)1234567890123(21)S123(10)3.0			NOT DONE	WARMUP PERIOD	DIURNAL	DHT-CAUSED

Row	SPDEVID	CRIT1	CRIT1FL	LBSTAT	LBREASND	ADTMCA1	AREASCA1
2976	(01)1234567890123(21)S123(10)3.0			NOT DONE	WARMUP PERIOD	DIURNAL	DHT-CAUSED
2977	(01)1234567890123(21)S123(10)3.0			NOT DONE	WARMUP PERIOD	DIURNAL	DHT-CAUSED
…							
4808	(01)1234567890123(21)S123(10)3.0					NOCTURNAL	
4809	(01)1234567890123(21)S123(10)3.0					NOCTURNAL	
4810	(01)1234567890123(21)S123(10)3.0					NOCTURNAL	
…							
4912	(01)1234567890123(21)S123(10)3.0					DIURNAL	
4913						DIURNAL	PARTICIPANT-CAUSED
4914						DIURNAL	PARTICIPANT-CAUSED
4915						DIURNAL	PARTICIPANT-CAUSED
4916						DIURNAL	PARTICIPANT-CAUSED
…							
5007						DIURNAL	PARTICIPANT-CAUSED
5008	(01)1234567890123(21)S123(10)5.0			NOT DONE	WARMUP PERIOD	DIURNAL	DHT-CAUSED
5009	(01)1234567890123(21)S123(10)5.0			NOT DONE	WARMUP PERIOD	DIURNAL	DHT-CAUSED

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Table A2. (Part 3) ADCGM Dataset Example

Row	DTYPE	AREASND	AELPDUR	AADJDTM	AELPDY	AHR	AMN	ADYWK
1		WARMUP PERIOD	P0DT8H0M	08Jan2024 8:00:00 AM	0	8	00	Monday
2		WARMUP PERIOD	P0DT8H5M	08Jan2024 8:05:00 AM	0	8	05	Monday
3		WARMUP PERIOD	P0DT8H10M	08Jan2024 8:10:00 AM	0	8	10	Monday
…		…						
23		WARMUP PERIOD	P0DT9H50M	08Jan2024 9:50:00 AM	0	9	50	Monday
24		WARMUP PERIOD	P0DT9H55M	08Jan2024 9:55:00 AM	0	9	55	Monday
25			P0DT10H0M	08Jan2024 10:00:00 AM	0	10	00	Monday
26			P0DT10H5M	08Jan2024 10:05:00 AM	0	10	05	Monday
27			P0DT10H10M	08Jan2024 10:10:00 AM	0	10	10	Monday
28			P0DT10H15M	08Jan2024 10:15:00 AM	0	10	15	Monday
29			P0DT10H20M	08Jan2024 10:20:00 AM	0	10	20	Monday
…								
49			P0DT12H0M	08Jan2024 12:00:00 PM	0	12	00	Monday
50			P0DT12H5M	08Jan2024 12:05:00 PM	0	12	05	Monday
51			P0DT12H10M	08Jan2024 12:10:00 PM	0	12	10	Monday
52			P0DT12H15M	08Jan2024 12:15:00 PM	0	12	15	Monday
…								
66			P0DT13H25M	08Jan2024 1:25:00 PM	0	13	25	Monday
67			P0DT13H30M	08Jan2024 1:30:00 PM	0	13	30	Monday
68			P0DT13H35M	08Jan2024 1:35:00 PM	0	13	35	Monday
…								
2022			P7DT7H55M	15Jan2024 7:55:00 AM	7	7	55	Monday
2023		WARMUP PERIOD	P7DT8H0M	15Jan2024 8:00:00 AM	7	8	00	Monday
2024		WARMUP PERIOD	P7DT8H5M	15Jan2024 8:05:00 AM	7	8	05	Monday
2025		WARMUP PERIOD	P7DT8H10M	15Jan2024 8:10:00 AM	7	8	10	Monday
…								
2045		WARMUP PERIOD	P7DT9H50M	15Jan2024 9:50:00 AM	7	9	50	Monday
2046		WARMUP PERIOD	P7DT9H55M	15Jan2024 9:55:00 AM	7	9	55	Monday
2047			P7DT10H0M	15Jan2024 10:00:00 AM	7	10	00	Monday
2048			P7DT10H5M	15Jan2024 10:05:00 AM	7	10	05	Monday

Row	DTYPE	AREASND	AELPDUR	AADJDTM	AELPDY	AHR	AMN	ADYWK
2049			P7DT10H10M	15Jan2024 10:10:00 AM	7	10	10	Monday
…								
2938			P10DT12H0M	18Jan2024 12:00:00 PM	10	12	00	Thursday
2939			P10DT12H5M	18Jan2024 12:05:00 PM	10	12	05	Thursday
2940			P10DT12H10M	18Jan2024 12:10:00 PM	10	12	10	Thursday
2941		SENSOR NOT ACTIVE	P10DT12H15M	18Jan2024 12:15:00 PM	10	12	15	Thursday
2942		SENSOR NOT ACTIVE	P10DT12H20M	18Jan2024 12:20:00 PM	10	12	20	Thursday
…								
2974		SENSOR NOT ACTIVE	P10DT15H0M	18Jan2024 3:00:00 PM	10	15	00	Thursday
2975		WARMUP PERIOD	P10DT15H12M	18Jan2024 3:12:00 PM	10	15	12	Thursday
2976		WARMUP PERIOD	P10DT15H17M	18Jan2024 3:17:00 PM	10	15	17	Thursday
2977		WARMUP PERIOD	P10DT15H22M	18Jan2024 3:22:00 PM	10	15	22	Thursday
…								
4808			P16DT23H57M	24Jan2024 11:57:00 PM	16	23	57	Wednesday
4809			P17DT0H2M	25Jan2024 12:02:00 AM	17	0	2	Thursday
4810			P17DT0H7M	25Jan2024 12:07:00 AM	17	0	7	Thursday
…								
4912			P17DT8H37M	25Jan2024 8:37:00 AM	17	8	37	Thursday
4913	PHANTOM	PARTICIPANT FORGOT	P17DT8H42M	25Jan2024 8:42:00 AM	17	8	42	Thursday
4914	PHANTOM	PARTICIPANT FORGOT	P17DT8H47M	25Jan2024 8:47:00 AM	17	8	47	Thursday
4915	PHANTOM	PARTICIPANT FORGOT	P17DT8H52M	25Jan2024 8:52:00 AM	17	8	52	Thursday
4916	PHANTOM	PARTICIPANT FORGOT	P17DT8H57M	25Jan2024 8:57:00 AM	17	8	57	Thursday
…								

Row	DTYPE	AREASND	AELPDUR	AADJDTM	AELPDY	AHR	AMN	ADYWK
5007	PHANTOM	PARTICIPANT FORGOT	P17DT16H32M	25Jan2024 4:32:00 PM	17	16	32	Thursday
5008		WARMUP PERIOD	P17DT16H35M	25Jan2024 4:35:00 PM	17	16	35	Thursday
5009		WARMUP PERIOD	P17DT16H40M	25Jan2024 4:40:00 PM	17	16	40	Thursday

6.3 Example ADaM Final Analysis Dataset (ADCGMEN Dataset)

Table A3 reports the final analysis dataset for the CGM-derived endpoints within a study. Within this example, a single CGM-derived endpoint for time in range is shown, where time in range is defined in the study documentation (not shown) as the percentage of epoch-level data within the target glucose range of 70-180 mg/dL. Within the ADCGMEN dataset, epoch-level data is collapsed based on AVISIT, which serves as the primary analysis timing variable for Study A; thus, individual epoch-level timepoints are omitted from the ADCGMEN dataset. Within the example, AVISIT is aggregated by week and a subset of the first four weeks of the study are shown for a single subject.

As defined in Table 4. Specifications for a Subset of ADCGMEN Variables and discussed in section 3.2.3.2 Handling of Missing ADaM Final Analysis Data, additional variables to support data quality are provided within the ADCGMEN dataset. Within the example, Valid Epochs (VALIDEPC) reports the total number of valid epochs for each AVISIT value and excludes epochs with null/empty CGM readings due to warmup periods or other CGM DHT issues. The Valid Percentage Expected (VALIDPCE) is calculated using VALIDEPC as the numerator and the total expected number of records by week as the denominator. In Study A, the denominator is calculated based on a five-minute epoch; thus, 288 epochs per day x 7 days a week = 2,016 expected epochs per week. Analysis Criterion and Criterion Evaluation Result Flag variables are used to indicate when the prespecified threshold of 70% is not met. Note that within Table A3 for AVISIT = 'Week 2' (Row 2), only 1,403 epochs (69.59%) were used to calculate time in range. In this example, AVAL is calculated even though 70% of epoch-level data was not available for Week 2, and CRIT1FL is set to 'Y'.

Table A3. Final Analysis Dataset Example

Row	USUBJID	PARAM	AVAL	AVISIT	VALIDEPC	VALIDPTE	CRIT1	CRIT1FL
1	A_100_1	Time in Range (%)	81.52890958	Week 1	1789	88.74%		
2	A_100_1	Time in Range (%)	88.41372209	Week 2	1403	69.59%	VALIDPCT < 70%	Y
3	A_100_1	Time in Range (%)	91.58240647	Week 3	1817	90.13%		
4	A_100_1	Time in Range (%)	90.09487666	Week 4	1802	89.38%		

6.4 Example ADaM Paired Glucose Analysis Dataset (ADGLUCPR Dataset)

Table A4, Parts 1 and 2, shows an example ADGLUCPR dataset that joins CGM epoch-level data with non-CGM glucose data as presented in section 3.2.4 ADaM Paired Glucose Analysis Dataset. Within Study A, a 15-minute window is defined in the SAP (not shown) such that CGM readings, for a minimum of 15 minutes before and after the non-CGM reading, are reported for each non-CGM reading within the ADGLUCPR dataset. Table A4 shows two primary scenarios within Rows 1-8 and by rows 9-16. Color coding is used to differentiate each scenario. Details for each scenario are described below:

- Rows 1-8 show the scenario where a non-CGM reading was taken on January 20, 2024, at 12:08 PM with a result of 186 mg/dL. Since the value exceeds the normal range of 180 mg/dL, NCGMCA1 = 'HYPERGLYCEMIA' for all non-CGM records.
    - When creating the ADGLUCPR dataset, a minimum of 15 minutes on either side of the 12:08 PM timestamp results in the subset of CGM readings collected from 11:50 AM through 12:25 PM. The results on these epochs are reported in CGMVAL with the datetime reported in CGMDTM.
    - CGMCA1 categorized the CGM readings based on the SAP (not shown) such that records within the target range of 70-180 mg/dL are considered 'normal'. Records below 70 are considered 'hypoglycemia' and those below 54 are considered 'severe hypoglycemia'. Records above 180 are considered 'hyperglycemia' and those above 250 are considered 'severe hyperglycemia'. Ranges and indicators should be clearly defined in the study SAP with supporting literature to define appropriate values.
        - Within the example, CGMCA1 = 'HYPERGLYCEMIA' for the CGM readings occurring between 12:05 PM and 12:20 PM.
    - Additional analysis variables presented in Table 5. Specifications for a Subset of ADGLUCPR Variables are also populated.
        - Absolute Difference (ABDIFF), Percent Difference (PCTDIFF), and Datetime Difference (DTMDIFF) are populated for all rows.
        - Closest Time Identifier (CDTMFL) is populated as 'Y' in Row 5 to indicate the CGM record captured closest in time to the non-CGM glucose record.
        - Closest Value Identifier (CVALFL) is populated as 'Y' in rows 4 and 7 to indicate the CGM record captured closest in value to the non-CGM glucose record. In this example, there are two records where CGMVAL = 183 mg/dL which is the closest value captured to the non-CGM glucose value of 186 mg/dL.

- Rows 9-16 represent a second scenario where an non-CGM glucose reading was taken on January 20, 2024, at 12:31 PM with a result of 170 mg/dL. Since the value no longer exceeds the normal range of 180 mg/dL, NCGMCA1 = 'NORMAL' for all records.
    - When creating the ADGLUCPR dataset, a minimum of 15 minutes on either side of the 12:31 PM timestamp results in epochs collected from 12:15 PM through 12:50 PM. The results on these epochs are reported in CGMVAL with the datetime reported in CGMDTM.
    - Similar variables are populated as described in scenario 1 for rows 1-8.

-

Table A4. (Part 1) ADGLUCPR Dataset Example

Row	USUBJID	NCGMPARM	NCGMVAL	NCGMCA1	NCGMDTM	NCGMID	CGMPARM	CGMVAL
1	A_100_1	Glucose (mg/dL)	186	HYPERGLYCEMIA	20Jan2024 12:08:00 PM	1	Glucose (mg/dL)	161
2	A_100_1	Glucose (mg/dL)	186	HYPERGLYCEMIA	20Jan2024 12:08:00 PM	1	Glucose (mg/dL)	172
3	A_100_1	Glucose (mg/dL)	186	HYPERGLYCEMIA	20Jan2024 12:08:00 PM	1	Glucose (mg/dL)	177
4	A_100_1	Glucose (mg/dL)	186	HYPERGLYCEMIA	20Jan2024 12:08:00 PM	1	Glucose (mg/dL)	183
5	A_100_1	Glucose (mg/dL)	186	HYPERGLYCEMIA	20Jan2024 12:08:00 PM	1	Glucose (mg/dL)	195
6	A_100_1	Glucose (mg/dL)	186	HYPERGLYCEMIA	20Jan2024 12:08:00 PM	1	Glucose (mg/dL)	190
7	A_100_1	Glucose (mg/dL)	186	HYPERGLYCEMIA	20Jan2024 12:08:00 PM	1	Glucose (mg/dL)	183
8	A_100_1	Glucose (mg/dL)	186	HYPERGLYCEMIA	20Jan2024 12:08:00 PM	1	Glucose (mg/dL)	175
9	A_100_1	Glucose (mg/dL)	170	NORMAL	20Jan2024 12:31:00 PM	2	Glucose (mg/dL)	190
10	A_100_1	Glucose (mg/dL)	170	NORMAL	20Jan2024 12:31:00 PM	2	Glucose (mg/dL)	183
11	A_100_1	Glucose (mg/dL)	170	NORMAL	20Jan2024 12:31:00 PM	2	Glucose (mg/dL)	175
12	A_100_1	Glucose (mg/dL)	170	NORMAL	20Jan2024 12:31:00 PM	2	Glucose (mg/dL)	172
13	A_100_1	Glucose (mg/dL)	170	NORMAL	20Jan2024 12:31:00 PM	2	Glucose (mg/dL)	169
14	A_100_1	Glucose (mg/dL)	170	NORMAL	20Jan2024 12:31:00 PM	2	Glucose (mg/dL)	167
15	A_100_1	Glucose (mg/dL)	170	NORMAL	20Jan2024 12:31:00 PM	2	Glucose (mg/dL)	168
16	A_100_1	Glucose (mg/dL)	170	NORMAL	20Jan2024 12:31:00 PM	2	Glucose (mg/dL)	164

Table A4. (Part 2) ADGLUCPR Dataset Example

Row	CGMVAL	CGMCA1	CGMDTM	CGMID	ABSDIFF	PCTDIFF	DTMDIFF	CDTMFL	CVALFL
1	161	NORMAL	20Jan2024 11:50:00 AM	1	25	13.44	PT18M		
2	172	NORMAL	20Jan2024 11:55:00 AM	2	14	7.53	PT13M		
3	177	NORMAL	20Jan2024 12:00:00 PM	3	9	4.84	PT8M		
4	183	HYPERGLYCEMIA	20Jan2024 12:05:00 PM	4	3	1.61	PT3M		Y
5	195	HYPERGLYCEMIA	20Jan2024 12:10:00 PM	5	9	4.84	PT2M	Y	
6	190	HYPERGLYCEMIA	20Jan2024 12:15:00 PM	6	4	2.15	PT7M		

Row	CGMVAL	CGMCA1	CGMDTM	CGMID	ABSDIFF	PCTDIFF	DTMDIFF	CDTMFL	CVALFL
7	183	HYPERGLYCEMIA	20Jan2024 12:20:00 PM	7	3	1.61	PT12M		Y
8	175	NORMAL	20Jan2024 12:25:00 PM	8	11	5.91	PT17M		
9	190	HYPERGLYCEMIA	20Jan2024 12:15:00 PM	6	20	11.76	PT16M		
10	183	HYPERGLYCEMIA	20Jan2024 12:20:00 PM	7	13	7.65	PT11M		
11	175	NORMAL	20Jan2024 12:25:00 PM	8	5	2.94	PT6M		
12	172	NORMAL	20Jan2024 12:30:00 PM	9	2	1.18	PT1M	Y	
13	169	NORMAL	20Jan2024 12:35:00 PM	10	1	0.59	PT4M		Y
14	167	NORMAL	20Jan2024 12:40:00 PM	11	3	1.76	PT9M		
15	168	NORMAL	20Jan2024 12:45:00 PM	12	2	1.18	PT14M		
16	164	NORMAL	20Jan2024 12:50:00 PM	13	6	3.53	PT19M		

6.5 Example Tables and Figures

Tables A5 and A6 show examples of data summary tables for Study A as described in section 4.0 Specifications for Tables and Figures. Within Table A5, the data completeness summary by planned treatment arm and Analysis Visit (AVISIT) is shown for weeks 1-4 while participants remain in the trial with active CGM use. Table A5 may be created using the ADCGMEN dataset (described in section 3.2.3 ADaM Final Analysis Dataset and shown in Appendix 6.3) or the ADCGM dataset (described in section 3.2.1 ADaM Epoch-Level Dataset and shown in Appendix 6.2). The dataset(s) used to create Table A5 should be clearly labeled in the submitted software programs (source code). Within Table A5, 'n' aligns with the total number of CGM readings present within the epoch-level data by treatment arm and AVISIT. For example, this may be calculated by totaling the number of rows where AVAL is not empty/null across participants by treatment arm and AVISIT in the ADCGM dataset, or by totaling values for Valid Epochs (VALIDEPC) across participants by treatment arm and AVISIT in the ADCGMEN dataset. The percentage (%) is calculated using 'n' as the numerator and the total number of expected epochs as the denominator for participants who remained in the trial with active CGM use. For example, the denominator may be calculated by totaling the number of rows across participants by treatment arm and AVISIT in the ADCGM dataset, or by totaling values for denominator used in calculating Valid Percentage Expected (VALIDPTE) in the ADCGMEN dataset across participants by treatment arm and AVISIT.

Table A5. Data Completeness Summary by Treatment Arm and Analysis Visit

Analysis Visit	Treatment	Placebo
Week 1	n (%)	n (%)
Week 2	n (%)	n (%)
Week 3	n (%)	n (%)
Week 4	n (%)	n (%)

Table A6 shows a missing data summary by planned treatment arm and reason to summarize which reason(s) contributes to the most amount of missing data. The table is derived using the ADCGM dataset (described in section 3.2.1 ADaM Epoch-Level Dataset and shown in Appendix 6.2). Reason is based on values of the Analysis Reason Not Performed (AREASND) variable or the Reason Not Performed (LBREASND) variable within the ADCGM dataset. Within Table A6, 'n' aligns with the total number of missing CGM readings within the epoch-level data by treatment arm and reason. For example, this may be calculated by totaling the number of rows where AVAL is empty/null across participants by treatment arm and reason in the ADCGM dataset. The percentage (%) is calculated using 'n' as the numerator and the total number of expected epochs as the denominator. For example, the denominator may be calculated by totaling the number of rows across participants by treatment arm and reason in the ADCGM dataset.

Table A6. Missing Data Summary by Treatment Arm and Reason

Reason[1]	Treatment	Placebo
Delay in Sensor Replacement	n (%)	n (%)
Accidental Sensor Removal	n (%)	n (%)
Data Transmission Issue	n (%)	n (%)
Data Upload Failure	n (%)	n (%)
Other File Corruption Issue	n (%)	n (%)
Reason Unknown	n (%)	n (%)

[1] The reasons for the missing epoch-level data shown in Table A6 are provided in the table as examples. The reason CGM data is missing should be provided based on collected data within the study. All reasons for noncompletion collected during the study should be included within the submitted table.