Emerging Digital Health Technology Data from Continuous Glucose Monitoring in Anti-Diabetic Product Clinical Trials

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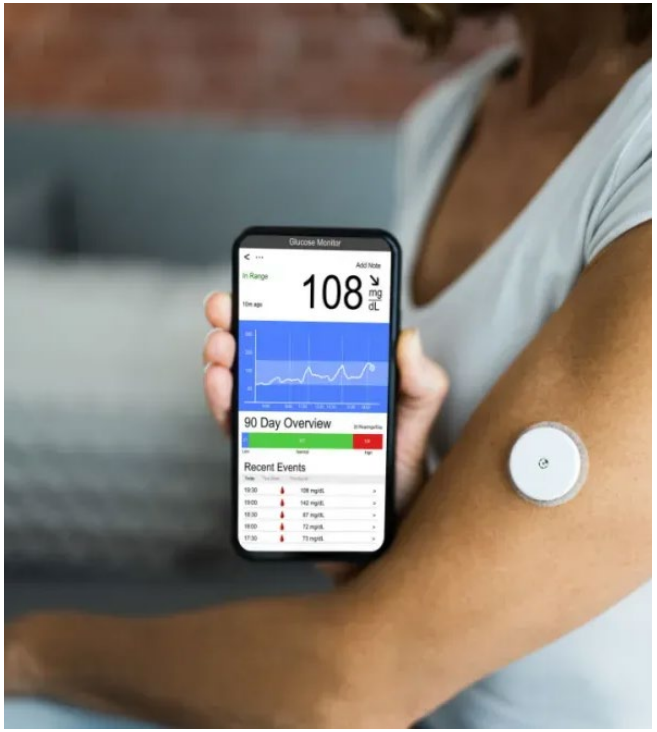


Disclaimer

- This presentation reflects the views of the author and should not be construed to represent FDA's views or policies

Outline

- Digital Health Technology
- Diabetes Mellitus
- Digital Health Technology in Anti-diabetic Product Clinical Trials
- Statistical Consideration for CGM Data
  - Data quality and integrity
  - CGM derived metrics
  - Missing data
- Concluding Remarks

DIGITAL HEALTH TECHNOLOGY

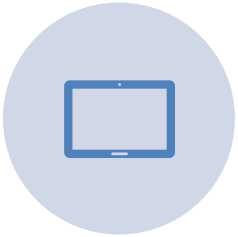
Digital Health Technology

- A digital health technology (DHT) is a system that uses computing platforms, connectivity, software, and/or sensors, for health care and related uses.

Glossary - BEST (Biomarkers, EndpointS, and other Tools) Resource - NCBI Bookshelf (nih.gov)

Types of DHTs

Mobile health apps and software



Wearable devices

Telehealth and telemedicine

Artificial intelligence and machine learning

Source: https://www.fda.gov/medical-devices/digital-health-center-excellence

DHT in Regulations

- Food and Drug Omnibus Reform Act of 2022 (FDORA)
  - Sec. 3606 Decentralized Clinical Studies
  - Sec. 3607 Modernizing Clinical Trials
- Prescription Drug User Fee Act VII (2023-2027)
  - IV.C. Enhancing use of DHTs to Support Drug Development and Review

PDFUA VII DHT Commitments

IV.C. Enhancing use of DHTs to Support Drug Development and Review

C.1 Develop Framework

C.2 Establish DHT Steering Committee

C.3 Convene 5 public meetings

C.4 Identify 3 demonstration projects

C.5 Develop Guidance

C.6 Develop Prescription Drug User-Related Software (PDURS) Guidance

C.7 Expand review capabilities

C.8 Enhance IT capabilities to review DHT-generated data

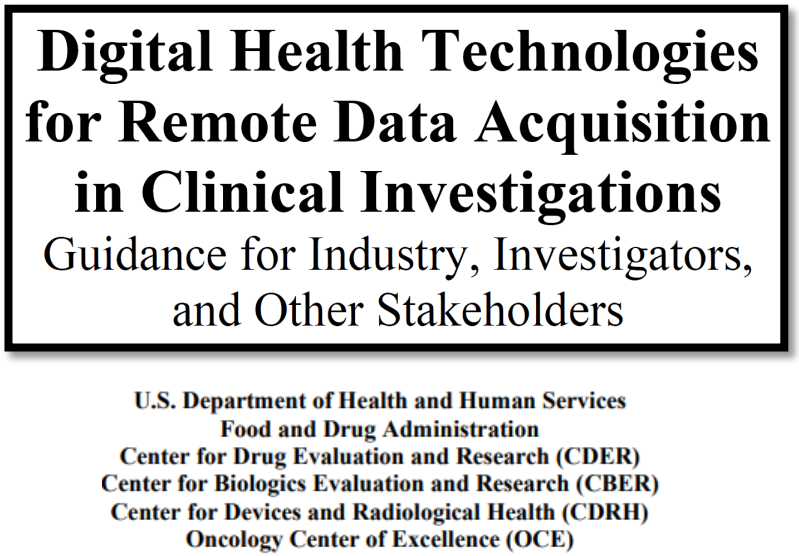
DHT Framework

Guide on
the use of DHT-derived data
in regulatory decision-makings
for drugs and biological products

- ✓ **Internal programs** (e.g., committee, training and expertise)
- ✓ **External programs** (e.g., guidance, public meetings)

Source: https://www.fda.gov/media/166396/download?attachment

FDA Guidance



- This guidance provides recommendations to facilitate the use of DHTs in clinical investigations for efficient medical product development to help bring new innovations and advances to patients
- Developed collaboratively across the Agency (e.g., drugs, biologics, and device)

Source: Digital Health Technologies for Remote Data Acquisition in Clinical Investigations | FDA

Fit-for-purpose of a DHT in Clinical Investigation

Verification: confirmation by examination and provision of objective evidence that the parameter that the DHT measures (e.g., acceleration, glucose value) ***is measured accurately and precisely.*** Verification is often viewed as part of the validation process

Validation: confirmation by examination and provision of objective evidence that the selected **DHT appropriately assesses the clinical event or characteristic** (e.g., step count or) *in the proposed participant population*

Source: Digital Health Technologies for Remote Data Acquisition in Clinical Investigations | FDA

DHT-Derived Endpoints

- **Endpoints***: A precisely defined variable intended to reflect an outcome of interest that is statistically analyzed to address a particular research question

- **Justification of novel endpoints**
  - Whether reflects how a participant feels, functions, or survives
  - Whether a biomarker as a surrogate endpoint will predict or will be reasonably likely to predict clinical benefit
  - Whether the endpoint effect is meaningful to the target patient population
  - How the endpoint relates to other endpoints that are intended to reflect the same concept and have been used to support a marketing authorization for a similar indication
  - Whether the novel endpoint is a well-defined and reliable measure of disease severity or health status (e.g., mild, moderate, or severe) to allow assessment of disease modification or progression.

Source: Digital Health Technologies for Remote Data Acquisition in Clinical Investigations | FDA
https://www.ncbi.nlm.nih.gov/books/NBK338448/

Statistical Considerations

- Same method/device for collection for all study arms
- Data quality
- Technical data specifications for readily analyzable DHT-derived data
- Algorithms used for summarizing, and analyzing DHT data
- Definitions used (e.g., glucose range, activity counts)
- Handling of missing data
- Estimand/Primary/Sensitivity analyses
- Difficulties in non-inferiority design due to defining NI margin

Source: Digital Health Technologies for Remote Data Acquisition in Clinical Investigations | FDA
https://www.ncbi.nlm.nih.gov/books/NBK338448/

Guidance Snapshot and Podcast

U.S. FOOD & DRUG ADMINISTRATION

Guidance Snapshot

Digital Health Technologies for Remote Data Acquisition in Clinical Investigations

Guidance for Industry, Investigators, and Other Stakeholders

What is recommended in this guidance?

This final guidance provides recommendations for sponsors, investigators, and other interested parties on the use of digital health technologies (DHTs) for remote data acquisition from participants in clinical investigations that evaluate medical products. The guidance focuses on recommendations for ensuring that a DHT is fit-for-purpose and that the level of validation associated with the DHT is sufficient to support the use, including the interpretability of its data, in the clinical investigation. This involves considerations of the DHT's form (i.e., design) and function(s) (i.e., distinct purpose within an investigation).

What is a DHT?

A DHT is a system that uses computing platforms, connectivity, software and/or sensors for health care and related uses. DHTs for remote data acquisition in clinical investigations can include hardware and/or software to perform one or more functions. They may rely on or work with other technologies that support their operation, such as general-purpose computing platforms (e.g., smartphones) and communication networks. Depending on the intended use of a DHT, the DHT may meet the definition of a device under the Federal Food, Drug, and Cosmetic Act (FD&C Act).

Why is this guidance important?

This guidance outlines recommendations intended to facilitate the use of DHTs in clinical investigations as appropriate for the evaluation of medical products. This guidance may improve the efficiency of clinical trials for sponsors, investigators, and other interested parties and may improve convenience and opportunities for individuals to participate in research. Increasing access to and use of DHTs in clinical trials can potentially enable the inclusion of diverse and underrepresented populations by facilitating decentralized clinical trials. Reducing the burden on trial participants can also improve trial recruitment, participant engagement, and retention throughout the study.

Examples of DHTs

www.fda.gov

Guidance Snapshots are a communication tool and are not a substitute for the guidance document. To learn more about DHTs, read the final Guidance. To see additional Guidance Snapshots, check out the pilot program.

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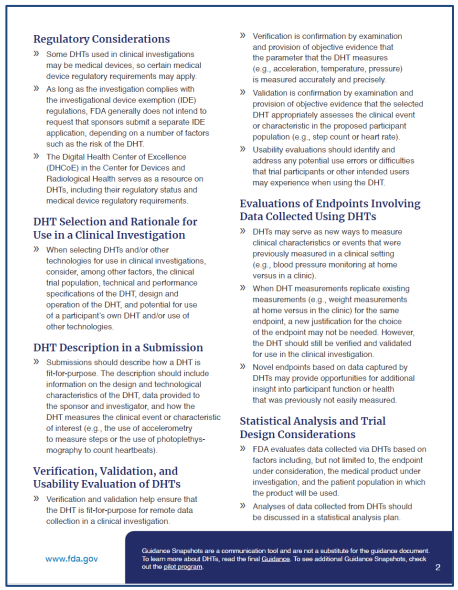

Regulatory Considerations

- Some DHTs used in clinical investigations may be medical devices, so certain medical device regulatory requirements may apply.
- As long as the investigation complies with the investigational device exemption (IDE) regulations, FDA generally does not intend to request that sponsors submit a separate IDE application, depending on a number of factors such as the risk of the DHT.
- The Digital Health Center of Excellence (DHCoE) in the Center for Devices and Radiological Health serves as a resource on DHTs, including their regulatory status and medical device regulatory requirements.

DHT Selection and Rationale for Use in a Clinical Investigation

- When selecting DHTs and/or other technologies for use in clinical investigations, consider, among other factors, the clinical trial population, technical and performance specifications of the DHT, design and operation of the DHT, and potential for use of a participant's own DHT and/or use of other technologies.

DHT Description in a Submission

- Submissions should describe how a DHT is fit-for-purpose. The description should include information on the design and technological characteristics of the DHT, data provided to the sponsor and investigator, and how the DHT measures the clinical event or characteristic of interest (e.g., the use of accelerometry to measure steps or the use of photoplethysmography to count heartbeats).

Verification, Validation, and Usability Evaluation of DHTs

- Verification and validation help ensure that the DHT is fit-for-purpose for remote data collection in a clinical investigation.
- Verification is confirmation by examination and provision of objective evidence that the parameter that the DHT measures (e.g., acceleration, temperature, pressure) is measured accurately and precisely.
- Validation is confirmation by examination and provision of objective evidence that the selected DHT appropriately assesses the clinical event or characteristic in the proposed participant population (e.g., step count or heart rate).
- Usability evaluations should identify and address any potential use errors or difficulties that trial participants or other intended users may experience when using the DHT.

Evaluations of Endpoints Involving Data Collected Using DHTs

- DHTs may serve as new ways to measure clinical characteristics or events that were previously measured in a clinical setting (e.g., blood pressure monitoring at home versus in a clinic).
- When DHT measurements replicate existing measurements (e.g., weight measurements at home versus in the clinic) for the same endpoint, a new justification for the choice of the endpoint may not be needed. However, the DHT should still be verified and validated for use in the clinical investigation.
- Novel endpoints based on data captured by DHTs may provide opportunities for additional insight into participant function or health that was previously not easily measured.

Statistical Analysis and Trial Design Considerations

- FDA evaluates data collected via DHTs based on factors including, but not limited to, the endpoint under consideration, the medical product under investigation, and the patient population in which the product will be used.
- Analyses of data collected from DHTs should be discussed in a statistical analysis plan.

www.fda.gov

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Risk Considerations When Using DHTs

- Sponsors, investigators, and institutional review boards (IRBs) should consider any risks to trial participants associated with use of the DHTs for data collection and should include them in the informed consent.
- The risks of using a DHT in a clinical investigation can generally be categorized as clinical risks and privacy-related risks.

Record Protection and Retention

- When using DHTs to record and transmit data during a clinical investigation, the relevant data captured from the DHT, including all relevant associated metadata, should be securely transferred to and retained in a durable electronic data repository as part of the record of the clinical investigation.
- The draft guidance for industry *Electronic Systems, Electronic Records, and Electronic Signatures in Clinical Investigations: Questions and Answers* addresses electronic records collected by DHTs during a clinical investigation.

Other Considerations When Using a DHT in a Clinical Investigation

- To help ensure the quality and integrity of data, adequate protection of participants, and satisfaction of regulatory requirements applicable to clinical investigations, sponsors and investigators should consider the sponsor's role, investigator's role, training, and impact of DHT updates and other changes.

www.fda.gov

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Insights About the Guidance

This guidance is being issued, in part, to satisfy the mandate under section 3607(a) of the Food and Drug Omnibus Reform Act of 2022 (FDORA) to issue guidance regarding the appropriate use of DHTs in clinical trials and meets a Prescription Drug User Fee Act (PDUFA) Reauthorization Performance Goal to finalize guidance on DHTs (section IV.C.5.b of the PDUFA VII commitment letter). Additional information on FDA's DHT PDUFA commitments is available on the webpage DHTs for Drug Development.

This guidance finalizes the draft guidance of the same title issued on December 23, 2021 (86 FR 72981). FDA considered comments received on the draft guidance as the guidance was finalized. Changes from the draft to the final guidance include clarification on the definition of DHTs and their function(s); further explanation on regulatory considerations for DHTs that meet the definition of a device under section 201(h) of the Federal Food, Drug, and Cosmetic Act; inclusion of references to Form FDA 1571 and Form FDA 356h for tracking submissions that include DHT data; and revisions to the Verification, Validation, and Usability Evaluations section.

Sponsors should engage early with the appropriate center responsible for the medical product under investigation to discuss the use of DHTs in a specific clinical investigation. The responsible center will consult other centers as needed. Sponsors should follow each FDA center's procedures for engaging with the Agency in the context of a development program.

Guidance Recap Podcast – Hear highlights straight from FDA staff

Speaker(s): Elizabeth Kunkoski, Consumer Safety Officer, Center for Drug Evaluation and Research and Anindita Saha, Associate Director for Strategic Initiatives, Digital Health Center of Excellence

Click here to listen

Click here to read transcript

www.fda.gov

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https://www.fda.gov/drugs/guidances-drugs/guidance-recap-podcast-digital-health-technologies-remote-data-acquisition-clinical-investigations

Quiz 1. Verification means confirming whether the DHT appropriately assesses the clinical event or characteristic in the proposed participant population.

(1) True
(2) False

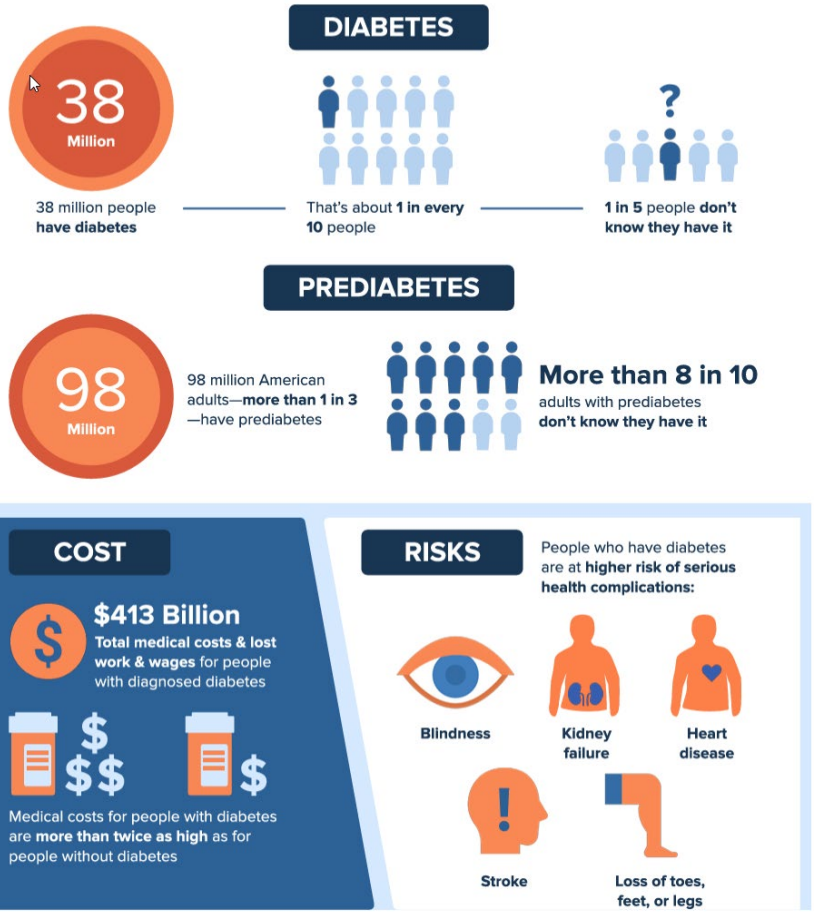
DIABETES MELLITUS

Diabetes Mellitus (DM)

Definition: A group of diseases that result in too much sugar in the blood (high blood glucose)

Types of Diabetes

- Type 1 DM
  - Body doesn't make enough insulin
- Type 2 DM
  - Body can't use insulin properly
- Gestational diabetes
  - Diabetes while pregnant



Source: https://www.cdc.gov/diabetes/communication-resources/diabetes-statistics.html

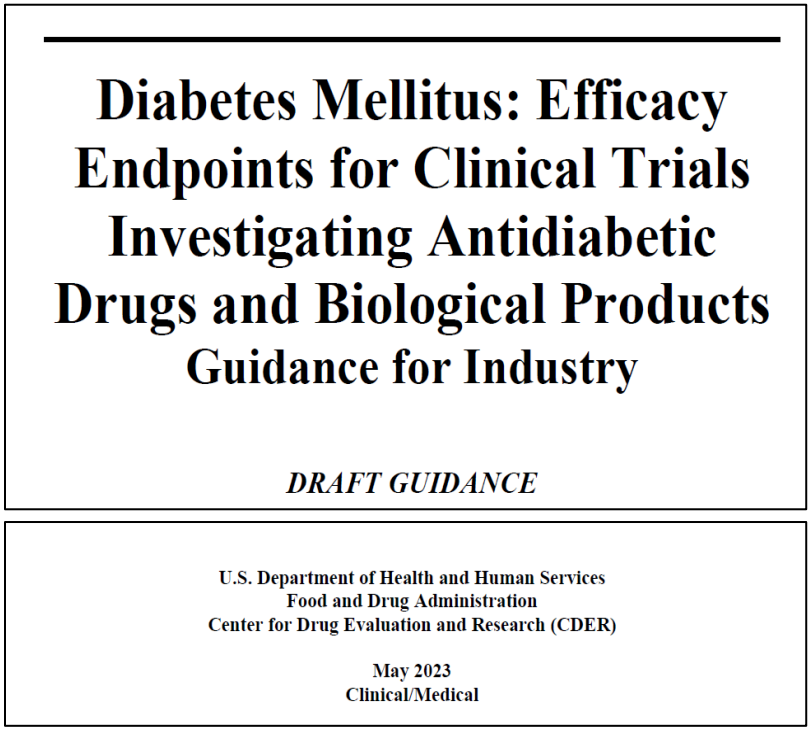
Antidiabetic Products for Treatment

Class	FDA approved products
Biguanide	metformin
DPP-4 inhibitors	alogliptin; linagliptin; saxagliptin; sitagliptin
GLP1 and dual GLP-1/GIP	dulaglutide; exenatide; liraglutide; lixisenatide; Injectable/oral semaglutide; tirzepatide
SGLT2 inhibitors	bexagliflozin, canagliflozin, dapagliflozin, ertugliflozin and empagliflozin
Sulfonylureas	limepiride, glipizide, and glyburide
Thiazolidinediones	rosiglitazone and pioglitazone
Insulin (rapid acting/long acting/ultra-long acting)	insulin human inhalation powder; insulin lispro ; insulin glargine injection; insulin lispro-aabc injection ; insulin aspart protamine and insulin aspart ; insulin degludec injection

https://diabetes.org/health-wellness/medication/oral-other-injectable-diabetes-medications

And more…

Clinical Trials for Antidiabetic Products



Diabetes Mellitus: Efficacy Endpoints for Clinical Trials Investigating Antidiabetic Drugs and Biological Products

Guidance for Industry

DRAFT GUIDANCE

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)

May 2023
Clinical/Medical

https://www.fda.gov/media/168475/download

- To help for antidiabetic drugs development aiming to improve glycemic control (i.e., hyperglycemia /hypoglycemia)
- **Efficacy endpoints** for antidiabetic product clinical trials
- **Hemoglobin A1c (A1C)**
  - A weighted average of blood glucose over the preceding 2 to 3 months
  - Reduction in A1C to be a **validated surrogate endpoint** for microvascular disease risk reduction adequate to support traditional drug approval

DIGITAL HEALTH TECHNOLOGY IN ANTI-DIABETIC PRODUCT CLINICAL TRIALS

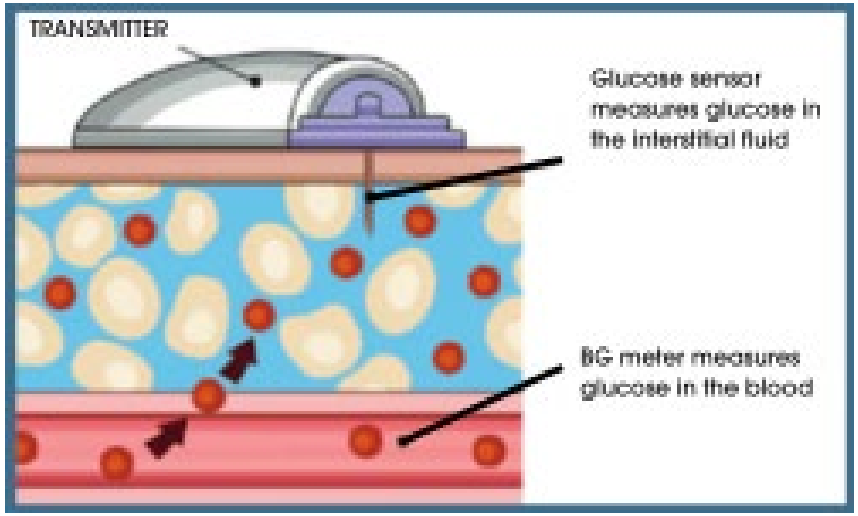
Continuous Glucose Monitoring (CGM)

- A wearable medical device that measures real-time blood glucose levels
- CGM for diabetes self-management
  - Easily tracked over time, and virtually monitored glucose values
  - To avoid hypoglycemia and hyperglycemia, inform dosing for prandial insulin and promote lifestyle change
- Approximately 40-50 % of patients with T1D are using CGM in practice
- CGM uptake for T2D is increasing rapidly in primary care
- Clinical practice recommends CGM as a part of diabetes management in patients with T1D or T2D on multiple daily injections or continuous subcutaneous insulin infusion*

*Reference: 2023 American Diabetes Association "Standards of Care"

CGM System

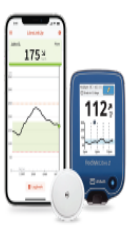
1. A sensor inserted under the skin to measure interstitial glucose
2. A transmitter that sends data from the sensor to a receiver or smartphone app,
3. A display device that shows real-time glucose readings



https://www.diabetesvic.org.au/back-to-basics-continuous-glucose-monitoring/

CGM Devices

CGM Options in the U.S. 2024


Abbott Libre 2


Abbott Libre 3


Dexcom G6


Dexcom G7


Dexcom Stelo


Eversense E3


Medtronic Guardian 3

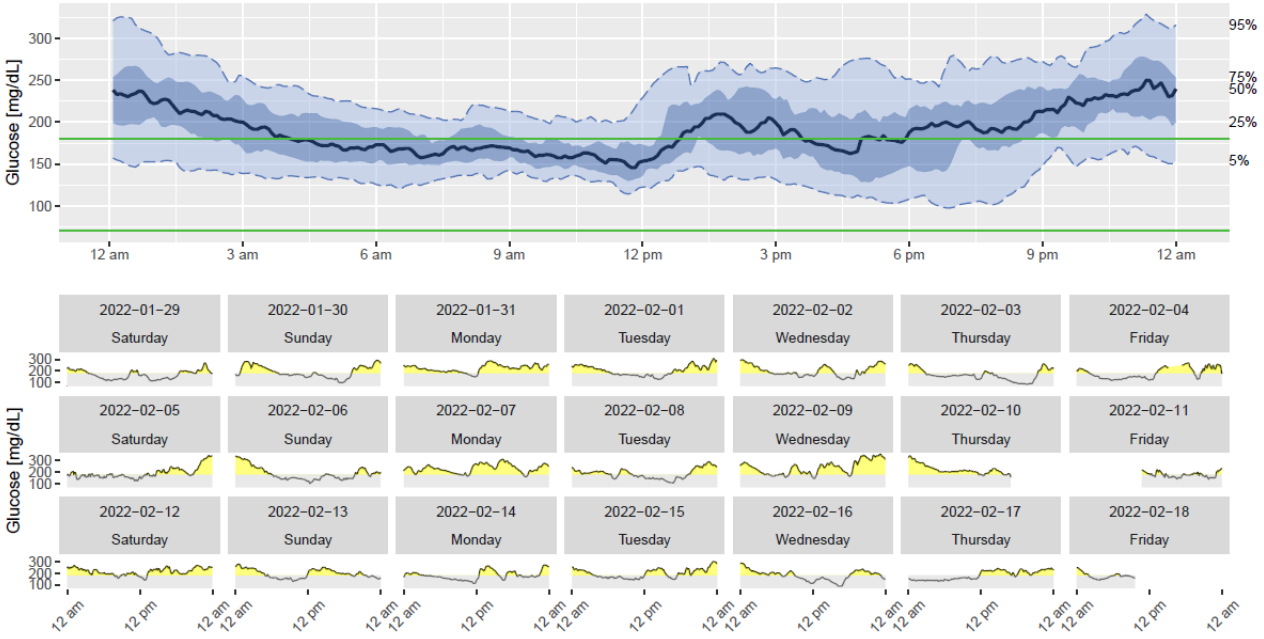

Medtronic Guardian 4

Sensor Wear Time	14 days	14 days	10 days	10 days	10 days	3-6 months*	7 days	7 days
Age Indication	4+ years		2 years +	2 years +	18 years+	18 years+	2+ years	7+ years
Sensor Readings	Every minute		Every 5 minutes			Every 5 minutes	Every 5 minutes	Every 5 minutes
Transmitter Style	Integrated	Integrated	Separate	Integrated	Integrated	Separate	Separate	Separate

Source: https://childrenwithdiabetes.com/continuous-glucose-monitoring/

CGM Data from Device

- Every 1 or 5 minutes readings produce 1440 or 288 data points per day
- Sensor wearing period (e.g., 10, 14, 21 days) produce high volume of granular data per subject



CGM-derived Endpoints

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FDA Guidance: Diabetes Mellitus: Efficacy endpoints for clinical trials investigating antidiabetic drugs and biologic products

https://www.fda.gov/media/168475/download

III. B.3.b Hypoglycemia

- Number of occurrences of low glucose values captured by a CGM system in a defined time period

III. C.3. CGM-Based metrics

- Time in "Ranges" defined as the percentage of time spent in a patient's target glucose range
  - Time between 70 and 180 mg/dL - Time in Range (TIR)
  - Time above range (time > 180 mg/dL)
  - Time below range (time < 70 mg/dL)
- TIR is a biomarker that has not been established as a surrogate for a clinical outcome. No long term prospective randomized control trial established relationship between micro/macrovascular outcome and TIR.

Fit-for-purpose of a **CGM** in Clinical Investigation

Verification:

CGM is measured accurately and precisely?

CGM vs reference

Assess impact of potential interferents

Assess software performance

Accuracy over intended period

Validation:

CGM appropriately assesses the clinical event or characteristic?

CGM derived endpoint under Context of Use (clear definition of what to measure)

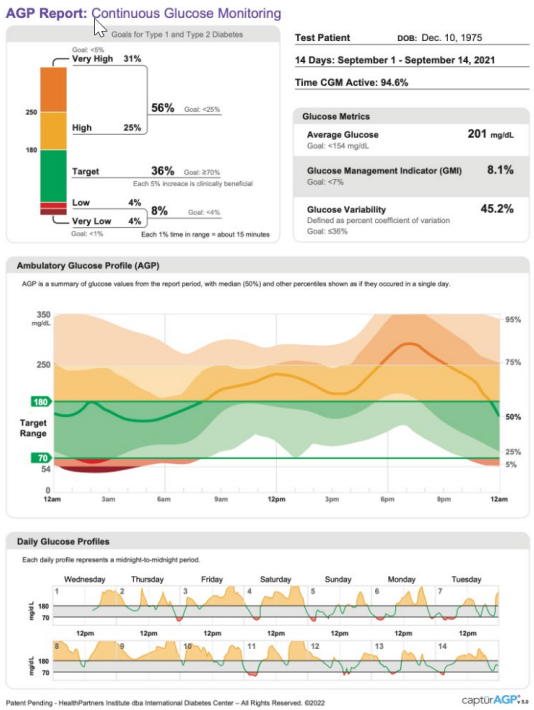
Assess the correlation with clinical outcome (clinical meaningfulness)

Assess reliability in intended population

Data collection/storage

Quiz 2. Which is currently validated efficacy endpoint for antidiabetic product clinical trial for glycemic control?

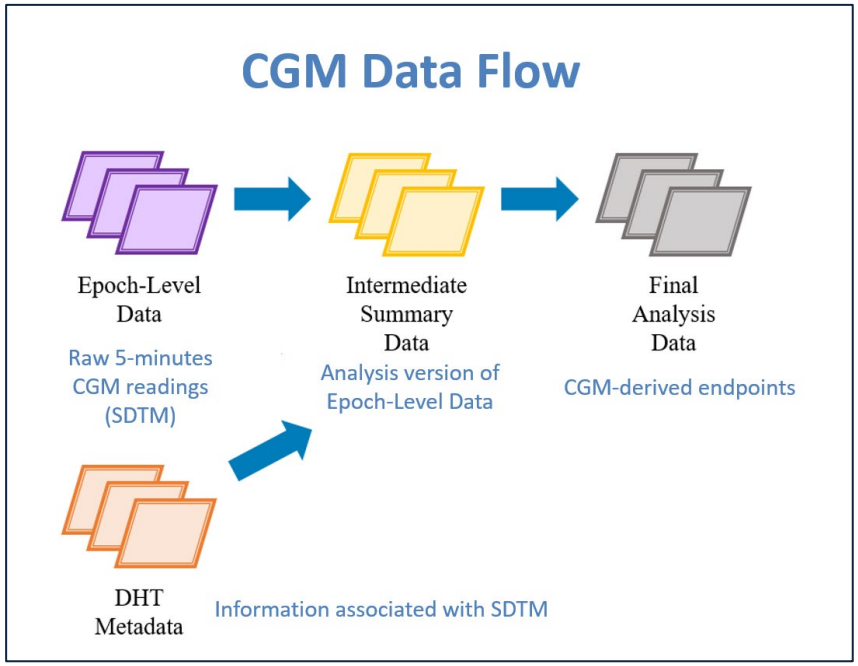
(1) Changes in A1C from baseline
(2) Changes in Time in Range from baseline



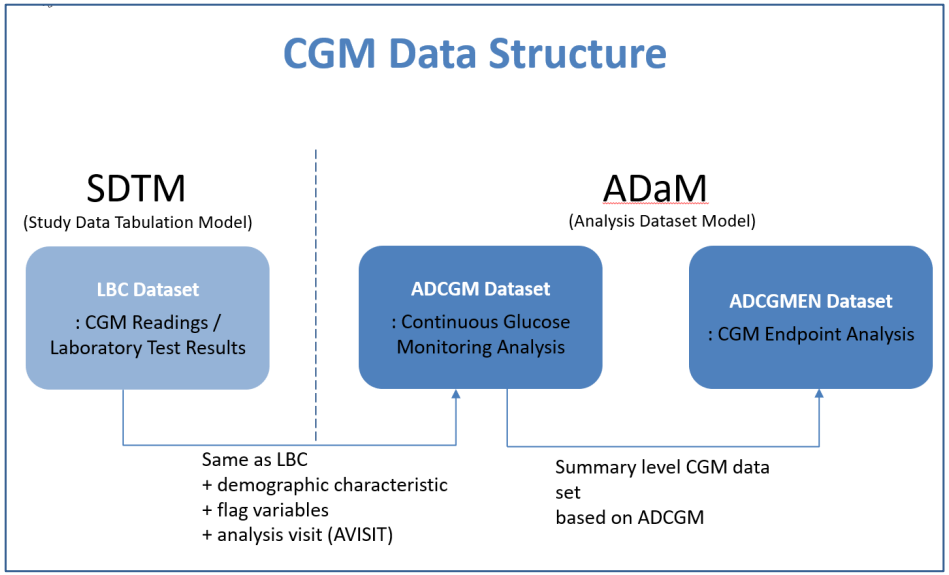
STATISTICAL CONSIDERATION FOR CGM DATA

DATA QUALITY AND INTEGRITY

CGM Data Flow/Structure



Credit: Hyesoo Cho (FDA/CDER/OB/DAI)



Credit: Hyesoo Cho (FDA/CDER/OB/DAI)

Data Quality and Integrity

- CGM metrics are derived from high volume CGM epoch-level data via several layers of data structures
  - Raw data (Epoch level, e.g., evert 5 min)
  - Intermediate summary data (e.g., daily, weekly)
  - Final analysis data (e.g., efficacy endpoints)
- Data quality and integrity check, and additional sensitivity analyses to ensure the reliable results of the final analysis for CGM derived endpoints due to several derivation steps

Example 1. Epoch-level Data Quality

- Example of randomized two arm study using 5-min interval reading device
- Checked for records time interval between two time points
- Duplicates possibly due to traveling, daylight saving, etc
- Need data quality check of these noises and prespecify the rules before unblinding data

CGM Records Time Interval	Arm 1, n (%)	Arm 2, n (%)
0-minute Interval	1 (0.00)	9 (0.00)
Between 1s and 4m 59s	528162 (14.95)	523409 (14.99)
Exact 5-minute Interval	2468238 (69.84)	2438333 (69.81)
Between 5m 1s and 9m 59s	536613 (15.18)	529959 (15.17)
Between 10m and Less than 1 day	955 (0.03)	1008 (0.03)

Example 2. Balance of Data Quality

- CGM device is verified through CDRH for systematic errors of device which could be inevitable
- Example of randomized two arm study using 7-day sensor device
- Checked for the number of sensors
- Need data quality check of these errors are at least balanced across arms

# Sensors during 28 days	Arm 1 (%)	Arm 2 (%)
1	1	0
2	1	2
3	4	4
4	35	34
5	53	50
6	5	8
7 and more	1	2

Example 3. Data Integrity- Merging

- Data integrity checking for possible errors while the merging datasets at several layers
- For example, when the epoch level data (SDTM) merging to specific visit variable or subject-level information to produce analysis ready data sets
  - Second level of time stamp (Hours:Minutes:Seconds) should be used for matching the epoch level data (e.g., 00:00:00 to 23:59:59) of the day matching to AVISIT
  - All epoch level data should be assigned to visit variable data to avoid being excluded from the final analysis dataset

CGM DERIVED METRICS

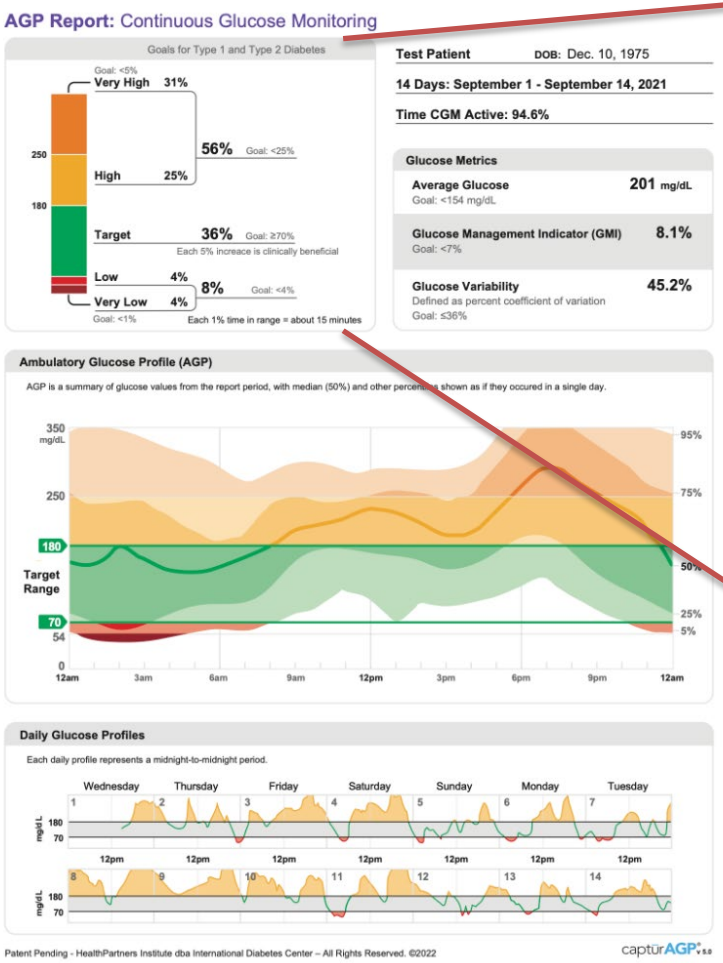
CGM Derived Metrics

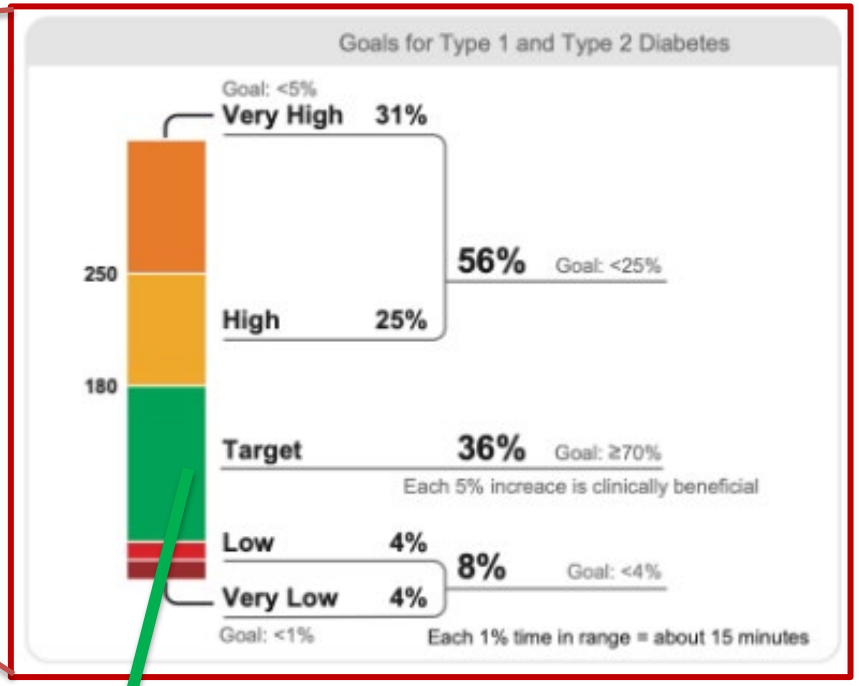
Unit	PARAM (Derived parameters)	Details
Count	Number of CGM readings	The total number of CGM readings
	Number of CGM readings with - Low IG (< 54 mg/dL, 54-70 mg/dL, < 70 mg/dL) - In Range (70-180 mg/dL) - High IG (> 180 mg/dL, 180-250 mg/dL, > 250 mg/dL)	The number of CGM readings in each range
% of readings	Time - < 54 mg/dL } Time Below Range (TBR) - < 70 mg/dL - In range (54-70 mg/dL) - **In range (70-180 mg/dL)** } Time In Range (TIR) - In range (180-250 mg/dL) - > 180 mg/dL } Time Above Range (TAR) - > 250 mg/dL	$\frac{\text{The number of CGM readings in the given glycemic range}}{\text{The total number of CGM readings}} \times 100$
Percentage	coefficient of variation (CV)	$\frac{\text{SD of glucose level}}{\text{Mean glucose level}} \times 100$

Abbreviation: CGM = continuous glucose monitoring; IG = interstitial glucose; SD = standard deviation

Credit: Hyesoo Cho (FDA/CDER/OB/DAI)

Use of CGM Metrics





Time in Range (70-180 mg/dL) (%)
e.g., Endpoint: change in TIR

AGP - Ambulatory Glucose Profile

http://www.agpreport.org/

CGM-detected Hypo/Hyperglycemia

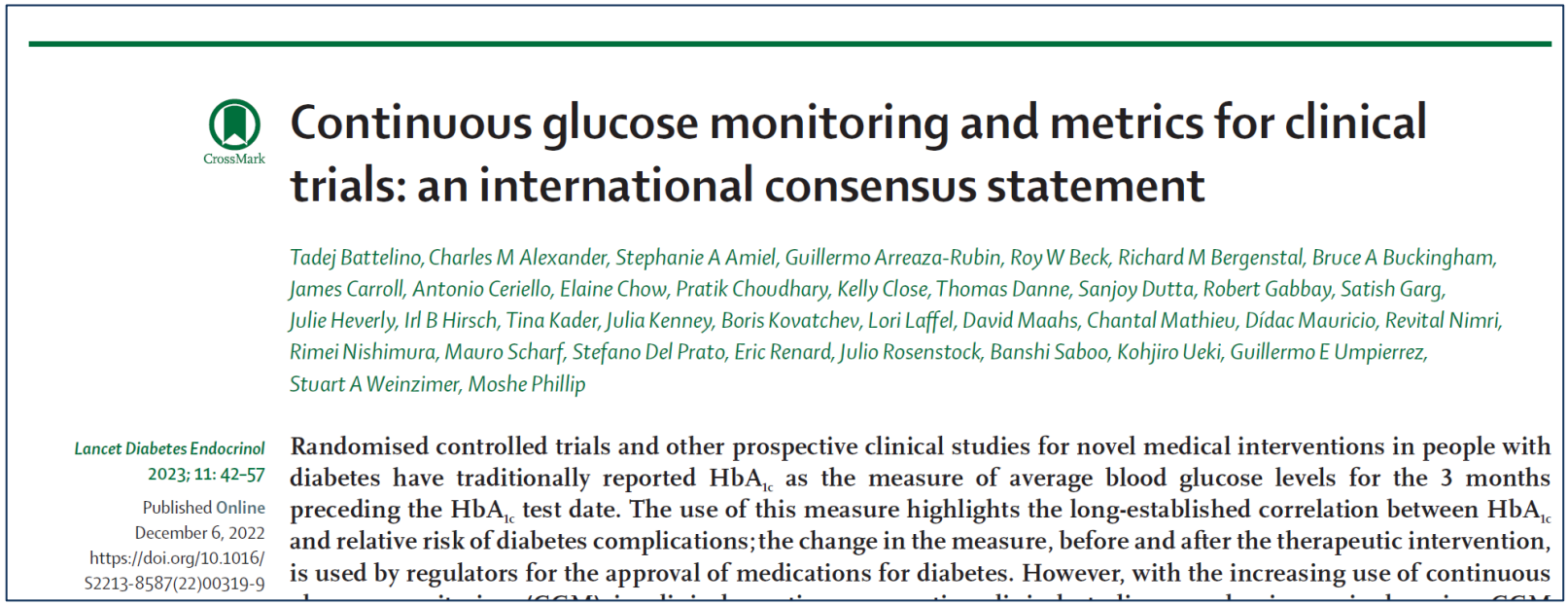
	Glycaemic criteria	Duration	Description
Hypoglycaemia	<70 mg/dL (<3·9 mmol/L), including readings of <54 mg/dL (<3·0 mmol/L)	≥15 consecutive min of <70 mg/dL	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose reducing therapy; event ends when there is ≥15 consecutive min with a CGM sensor value of ≥70 mg/dL
Hypoglycaemia alert value (Level 1)	54–69 mg/dL (3·0–3·9 mmol/L)	≥15 consecutive min of <70 mg/dL	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose reducing therapy; event ends when there is ≥15 consecutive min with a CGM sensor value of ≥70 mg/dL
Clinically significant hypoglycaemia (Level 2)	<54 mg/dL (< 3·0 mmol/L)	≥15 consecutive min	Serious, clinically important hypoglycaemia; event ends when there is ≥15 consecutive min with a CGM sensor value of ≥54 mg/dL
Extended hypoglycaemia	<70 mg/dL (<3·9 mmol/L)	>120 consecutive min	No maximum agreed duration; during periods of extended hypoglycaemia, any periods of hypoglycaemia <54 mg/dL should be reported separately
High glucose (Level 1)	181–250 mg/dL (10·1–13·9 mmol/L)	≥15 consecutive min	Event ends when there is ≥15 consecutive min with a CGM sensor value of ≤180 mg/dL
Very high glucose (Level 2)	>250 mg/dL (>13·9 mmol/L)	≥15 consecutive min	Event ends when there is ≥15 consecutive min with CGM sensor value of ≤250 mg/dL
Extended hyperglycaemia	>250 mg/dL (>13·9 mmol/L)	≥90 cumulative min within a 120-min period	Often postprandial

Other non-CGM measures of symptomatic hypoglycaemia can be recorded and might be correlated with CGM-derived measures. When reporting or evaluating the frequency of hypoglycaemia with sensor glucose values, low sensor glucose values can be asymptomatic in people with diabetes and might be evident in people without diabetes,[81] especially values between 60–70 mg/dL (3·0–3·9 mmol/L). In a clinical trial, assumptions concerning impaired awareness of hypoglycaemia should be confirmed with a validated tool.[82] Severe hypoglycaemia cannot be classified by CGM-derived data, it is a clinical diagnosis defined by severe cognitive impairment requiring external assistance for recovery, and not by a specific glucose threshold.

Table 4: **Classification of CGM-detected hypoglycaemia or hyperglycaemia to be counted in clinical trials**

https://www.thelancet.com/journals/landia/article/PIIS2213-8587(22)00319-9/fulltext

CGM Consensus Statement 2023



Continuous glucose monitoring and metrics for clinical trials: an international consensus statement

Tadej Battelino, Charles M Alexander, Stephanie A Amiel, Guillermo Arreaza-Rubin, Roy W Beck, Richard M Bergenstal, Bruce A Buckingham, James Carroll, Antonio Ceriello, Elaine Chow, Pratik Choudhary, Kelly Close, Thomas Danne, Sanjoy Dutta, Robert Gabbay, Satish Garg, Julie Heverly, Irl B Hirsch, Tina Kader, Julia Kenney, Boris Kovatchev, Lori Laffel, David Maahs, Chantal Mathieu, Dídac Mauricio, Revital Nimri, Rimei Nishimura, Mauro Scharf, Stefano Del Prato, Eric Renard, Julio Rosenstock, Banshi Saboo, Kohjiro Ueki, Guillermo E Umpierrez, Stuart A Weinzimer, Moshe Phillip

Lancet Diabetes Endocrinol 2023; 11: 42–57

Published Online December 6, 2022 https://doi.org/10.1016/S2213-8587(22)00319-9

Randomised controlled trials and other prospective clinical studies for novel medical interventions in people with diabetes have traditionally reported HbA_{1c} as the measure of average blood glucose levels for the 3 months preceding the HbA_{1c} test date. The use of this measure highlights the long-established correlation between HbA_{1c} and relative risk of diabetes complications; the change in the measure, before and after the therapeutic intervention, is used by regulators for the approval of medications for diabetes. However, with the increasing use of continuous

* ADA's grading system for evidence level to support each recommendation

- **A**—Clear evidence from well-conducted, generalizable randomized controlled trials that are adequately powered
- **B**—Supportive evidence from well-conducted cohort studies
- **C**—Supportive evidence from poorly controlled or uncontrolled studies
- **E**—Expert consensus or clinical experience

https://www.thelancet.com/journals/landia/article/PIIS2213-8587(22)00319-9/fulltext

The Application of CGM in a Clinical Trial Setting

- CGM data should be collected at baseline and at all specified study timepoints with the CGM device selected for the clinical trial (E)
- CGM should be used for a minimum of 14 consecutive days every 3 months throughout the study, including at baseline (B)
  - The aim is that a minimum of 70% of the glucose data should be obtained for each individual participant
  - All CGM data should be included in the final analysis, but the proportion of participants who met the minimum 70% data obtainment requirement during 14 days should also be reported as part of the data completeness

https://www.thelancet.com/journals/landia/article/PIIS2213-8587(22)00319-9/fulltext

Interpretation of TIR Difference

- Studies can be powered to detect a minimum 3% change in mean time in range between study groups (E)
- A difference of 5% in TIR is considered clinically meaningful for an individual participant in a clinical study and 3% is considered clinically meaningful for a treatment group difference in mean TIR (E)
- Of note, TIR is not a validated endpoint.

https://www.thelancet.com/journals/landia/article/PIIS2213-8587(22)00319-9/fulltext

CGM Data in the Final Analysis Set

- All CGM data should be included in the analysis set (E)
- Managing **missing data** should be part of the statistical analysis plan so that no CGM data are excluded from the final analysis set (E)

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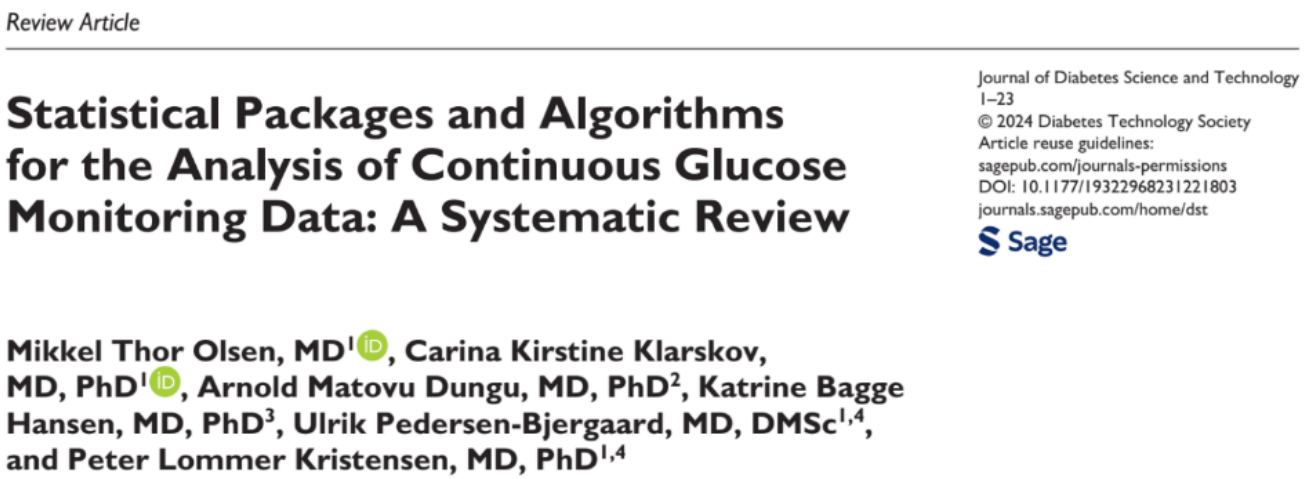
Available Packages for CGM Data Analysis



Review Article

Statistical Packages and Algorithms for the Analysis of Continuous Glucose Monitoring Data: A Systematic Review

Journal of Diabetes Science and Technology
1–23

DOI: 10.1177/19322968231221803
journals.sagepub.com/home/dst
Sage

Mikkel Thor Olsen, MD[1], Carina Kirstine Klarskov, MD, PhD[1], Arnold Matovu Dungu, MD, PhD[2], Katrine Bagge Hansen, MD, PhD[3], Ulrik Pedersen-Bjergaard, MD, DMSc[1,4], and Peter Lommer Kristensen, MD, PhD[1,4]

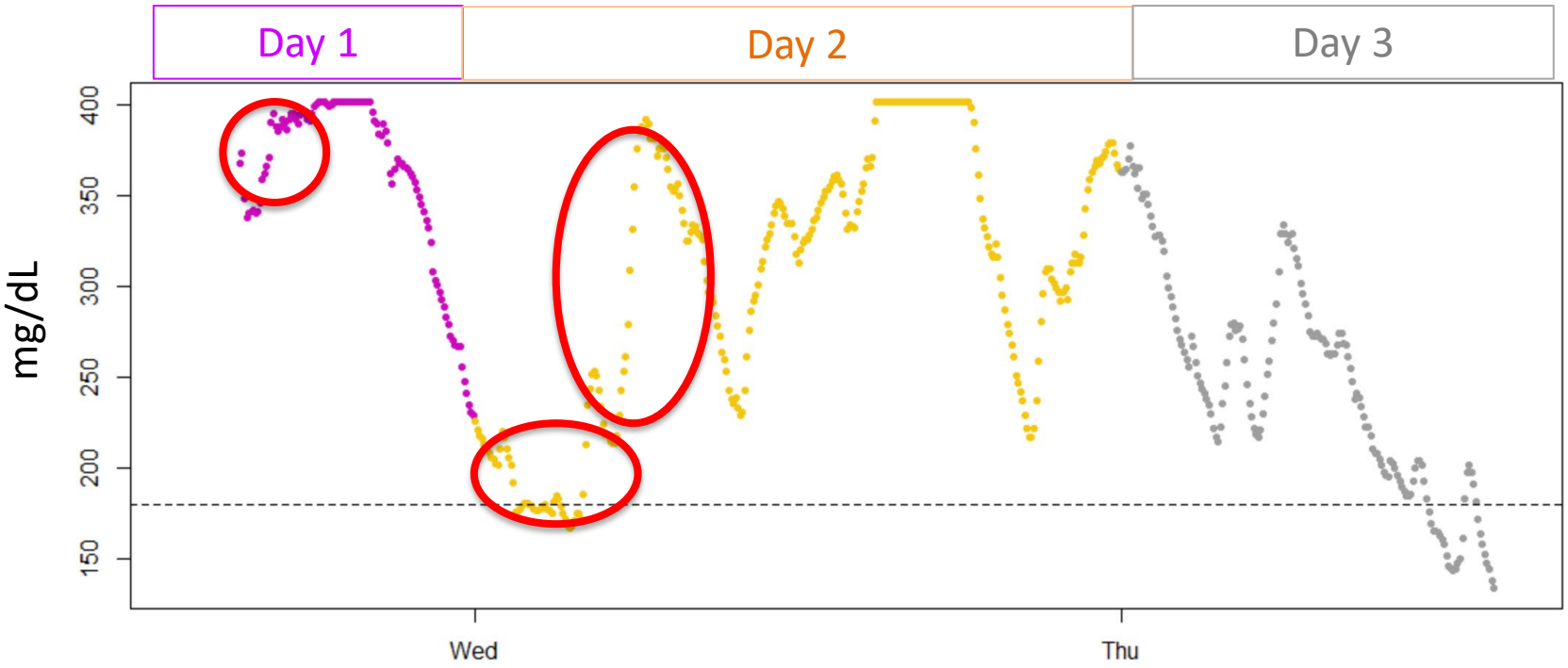
- 23 software packages
- 11 packages can impute missing data (simple and different approaches: mean, linear interpolation)
- iglu, cgmanalysis, AGATA could calculate most of 2023 CGM consensus metrics

https://journals.sagepub.com/doi/10.1177/19322968231221803?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

MISSING DATA

Missing Data – Epoch level

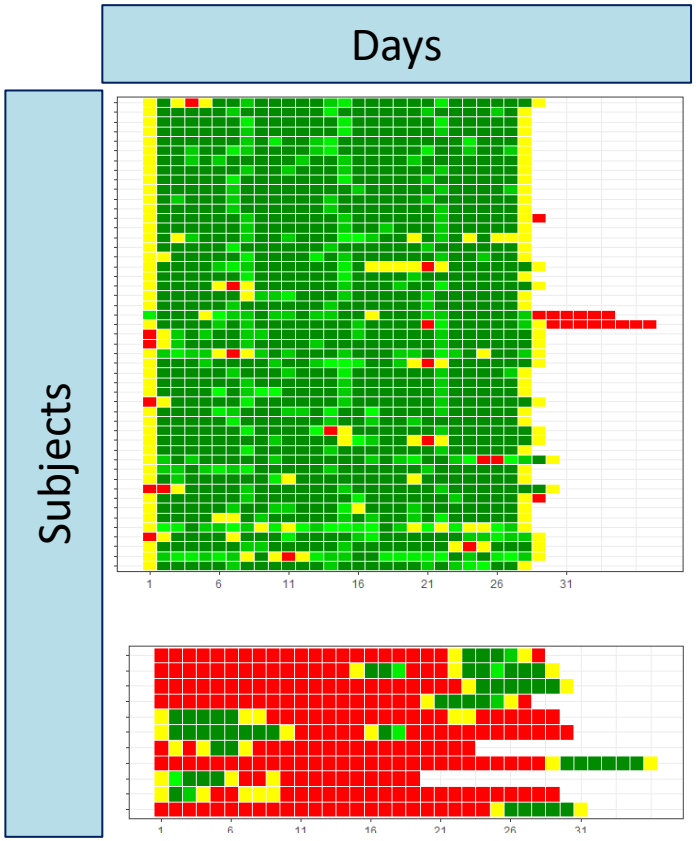
- Example of one subject (hyperglycemia) for 3 days wear



Missing Data – Daily level

Subjects who have 28 days of CGM data

Subjects who have less than 14 days of CGM data



CGM Readings

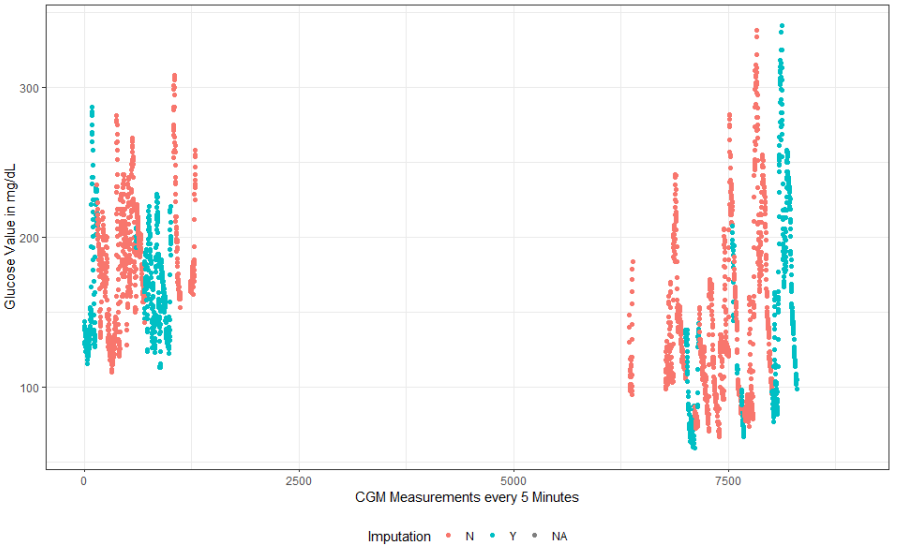
- 100%
- 90-100%
- 80-90%
- 70-80%
- < 70%
- No CGM recordings

Credit: Hyesoo Cho (FDA/CDER/OB/DAI)

Example: Missing Data Imputation – epoch level

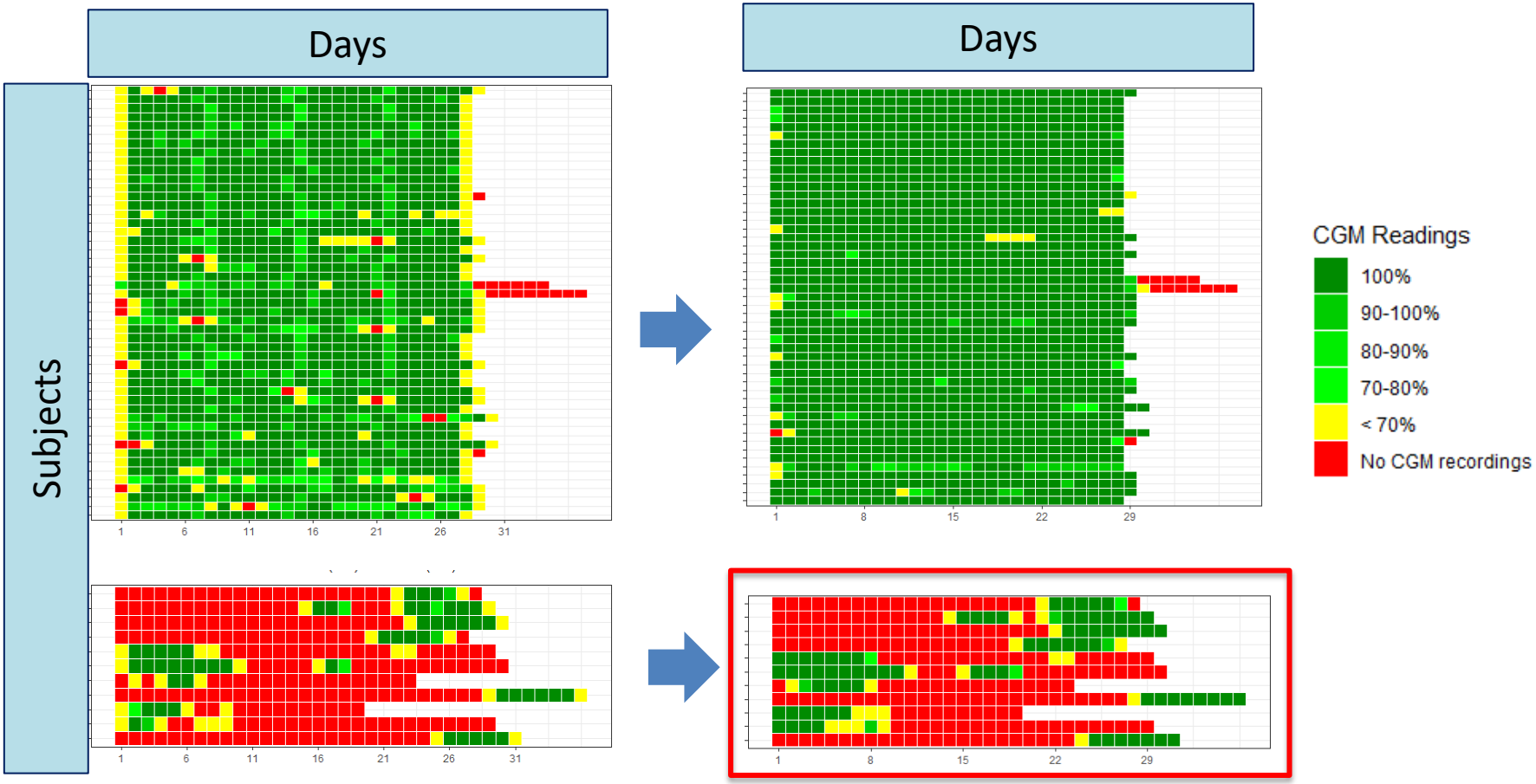
CGM Missing rate ≈ 10%

CGM Missing rate ≈ 80%



- As an example, non-missing epoch-level values (red points) and imputed values (blue points) for missing epoch-level values were plotted across time period.
- Missing values were interpolated (blue points) using a daycycle method in the CGManalyzer R package.
- There are limitation of imputing epoch-level missing data if the breakage between data points are longer period (e.g., right panel: overall CGM missing rate of 80%).

Before and After
Epoch-level Missing Data Imputation



Missing data- CGM-Derived Endpoints

- CGM-derived endpoints are defined by the time-period of days (e.g., Change from baseline in Time in Range (%) at Weeks 22 to 26; TIR endpoint)
- For reliable derivation of CGM-derived endpoint in the time-period, minimum valid days (e.g., 10 days) are needed.
- CGM-derived endpoints of subjects who do not have CGM data during the entire time-period, or who have CGM data during less than minimum valid days in the time-period are considered as missing.
- Appropriate method to handle missing data under the specified esitmand should be pre-specified to CGM-derived endpoint (e.g., imputing the missing TIR endpoint using retrieved dropouts under estimand using treatment policy strategy*).
- Sensitivity analyses to check the impact of missingness at different level are necessary.

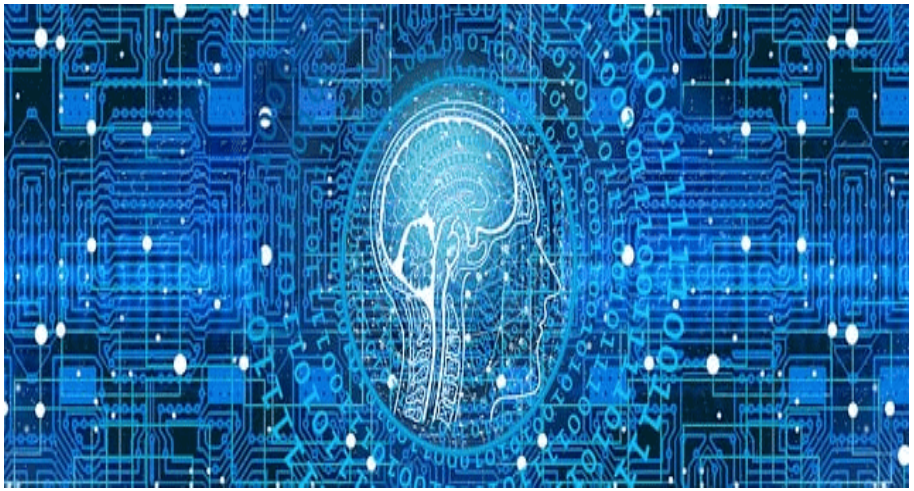
*Wang et al. (2023) https://onlinelibrary.wiley.com/doi/10.1002/pst.2299

Quiz 3. For CGM data analysis from clinical trials, what statistical aspects should be considered?

(1) Data quality
(2) Data integrity
(3) Missing data handling
(4) All above

Quiz 4. In clinical trial investigating antidiabetic products for glycemic control in adults with type 2 diabetes, CGM-derived metrics can be considered as endpoints.

(1) True
(2) False



CONCLUDING REMARKS

Summary

- The use of DHT including CGM device is blooming in clinical trial settings.
- Verification and validation of DHT are necessary steps to check the fit-for-purpose of DHT derived endpoints in clinical trials for regulatory submissions.
- DHT data quality and integrity should be investigated for reliable derivation of DHT-derived endpoints.
- Statistical consideration including clear definition of endpoints, estimand, handling missing data and analysis methods to evaluate DHT-derived endpoints should be preplanned for clinical trials.

Recommendation for CGM data in Regulatory Submission

- The study protocol and SAP should pre-specify details regarding the algorithms for summarizing (i.e., clear definition of CGM-derived endpoints) and analyzing CGM-based data (i.e., estimand, analysis model), and the statistical methods to assess and handle missing CGM data (e.g., at epoch-level, daily level, and summary level).

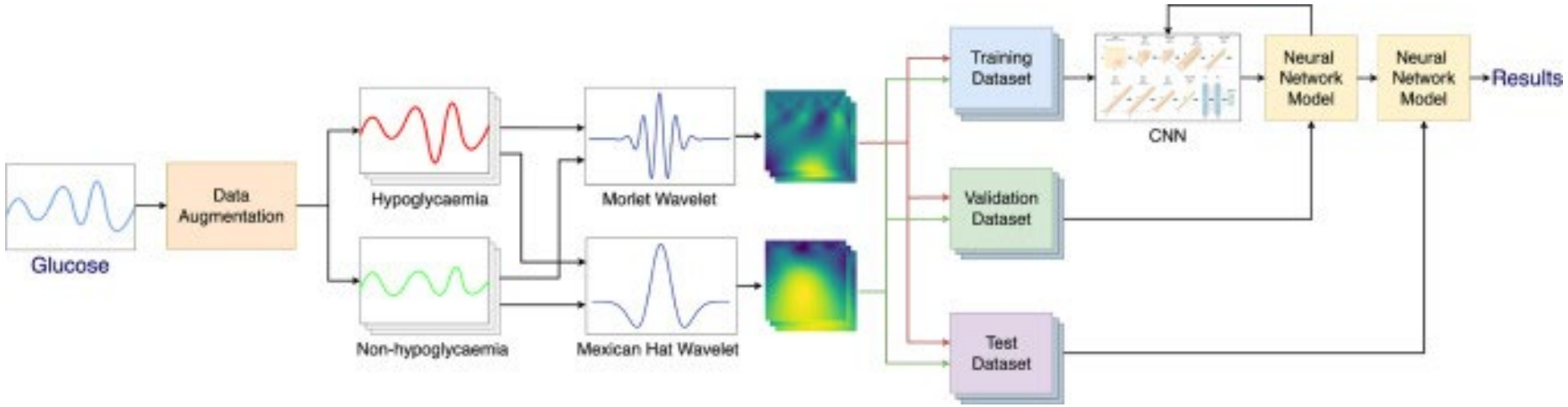
- All source data including SDTM datasets (e.g., epoch-level data) and metadata used to create the ADaM datasets (e.g, epoch-level, intermediate-level (i.e., daily), and summary-level (i.e. endpoint) with additional variables (e.g., timing variable)) along with the programming codes are needed for data quality and integrity check across derivation steps.

More to Come…
Future Use of CGM data

Combining wavelet transform with convolutional neural networks for hypoglycemia events prediction from CGM data

Jorge Alvarado [a,*], J. Manuel Velasco [b], Francisco Chavez [a], Francisco Fernández-de-Vega [a], J. Ignacio Hidalgo [b]

[a] *Universidad de Extremadura, Santa Teresa de Jornet 38, Mérida, Spain*
[b] *Universidad Complutense de Madrid, Profesor José García Santesmases 9, Madrid, Spain*



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- FDA/CDER/OTS/OB/DAI & DBVII:
  - Hye Soo Cho (DAI), Matilde Kam(DAI)
  - Tae Hyun Chung (DBVII)
- ORISE summer interns: Tong Qi , Qi Yu


FDA
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ADMINISTRATION

BACKUP

CGM Device Selection for Use in Clinical Trials

- The same brand and model of CGM device should be used throughout a clinical study to ensure consistent technical characteristics and sensor bias within the study (B)
- The accuracy performance characteristics of any CGM device selected for use in a clinical study should be reviewed during study protocol development before the study begins, including ethnic and racial inclusivity to evaluate whether it meets the needs of the study population and endpoints (E)

https://www.thelancet.com/journals/landia/article/PIIS2213-8587(22)00319-9/fulltext

CGM Data Analysis Packages

TABLE 1. OVERVIEW INFORMATION OF SOFTWARE PACKAGES FOR CONTINUOUS GLUCOSE MONITORING DATA ANALYSIS

Name	*GlyCulator*	*EasyGV*	*CGM-GUIDE©*	*GVAP*	*Tidepool*	*CGManalyzer*	*cgmanalysis*	*GLU*	*CGMStatsAnalyser*	*iglu*	*rGV*	*cgmquantify*
Year of analyzed version	October, 2021	October, 2020	December, 2011	April, 2015	September, 2015	January, 2018	October, 2019	February, 2020	January, 2021	April, 2021	July, 2021	August, 2021
GUI	Yes	Yes	Yes	Yes	Yes	No	No	No	Yes	Yes	Yes	No
Available	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Open source	No[a]	No	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Citations	68	221	24	19	29	17	23	4	0	5	0	1
Programming language[b]	R	Mi	Mat 2008b	Mat 2010b	JS	R	R	R	App	R	R	R, Py
Supported devices[c]	Any[d]	Any[d]	Any[d]	Any[d]	11	AbbF, Glut, Dex, Med+any[d]	Dia, Dex, Med iPro 2, CL, AbbF +any[d]	Med iPro2, AbbF, Dex G6+any[d]	Med iPro2+any[d]	Dex, AbbF, AbbP, Med, iPro+any[d]	Any[d]	Dex, AbbF +any[d]
Data format	csv, txt, xls, xlsx	xlsm	xls	xls	d.s.	d.s.	csv	csv	csv	csv	csv	csv
Data frame	Time, CGM	CGM	Time, CGM	Date, Time, CGM, Index	d.s.	d.s.	Id, Time, CGM	Time, CGM	Time, CGM	Id, Time, CGM	Time, CGM	CGM, Time, day
Input units	mg/dL, mmol/L	mmol/L	mg/dL	mg/dL	mg/dL, mmol/L	mg/dL, mmol/L	mg/dL	mmol/L	mmol/L	mg/dL	mg/dL	mg/dL
Complexity for data upload	Low	Low	—	Med.	—	High	Med.	Med.	Med	Med.	Med.	Med.
Download reports/data extraction	Yes	Yes	—	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Units' conversion	Yes	To mmol/L	No	No	Yes	No	No	No	No	No	n.a.	Yes
Documentation	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Updating	Yes	Yes	No	No	Yes	Yes	Yes	Yes	New	Yes	New	New
Toy example	Yes	Yes	No	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Video tutorial	Yes	No	No	No	Yes	No	No	No	No	No	No	No

Number of citations provided is based on Scopus (latest search May 2022).
[a]GlyCulator source code available only for the previous versions.
[b]Programming languages: R, Microsoft (Mi), Matlab (Mat), Javascript (JS), Java (J), and Python (Py).
[c]Supported devices: Abbott FreeStyle Libre (AbbF), Glutalor (Glut), Dexcom (Dex), Medtronic (Med), Diasend (Dia), Carelink (CL), and Abbott FreeStyle Libre Pro (AbbP).
[d]Any device is accepted after conversion to a general format.
—, Not available information; CGM, continuous glucose monitoring; d.s., device specific; GUI, Graphical User Interface; med., medium; n.a., not available.

Piersanti et al., 2023.Diabetes Technology & Therapeutics, 25(1), pp.69-85
https://www.liebertpub.com/doi/10.1089/dia.2022.0237?url_ver=Z39.88-2003&rfr_id=ori:rid:crossref.org&rfr_dat=cr_pub%20%200pubmed

	Units and quantity
Core endpoints	
Time in range 70–180 mg/dL (3·9–10·0 mmol/L)	Percentage of time in range; amount of time (hours and minutes)
Time below range <70 mg/dL (<3·9 mmol/L), including readings of <54 mg/dL (<3·9 mmol/L)	Percentage of time below range; amount of time (hours and minutes)
Time below range <54 mg/dL (<3·0 mmol/L)	Percentage of time below range; amount of time (hours and minutes)
Time above range >180 mg/dL (>10·0 mmol/L), including readings of >250 mg/dL (<13·9 mmol/L)	Percentage of time above range; amount of time (hours and minutes)
Time above range >250 mg/dL (>13·9 mmol/L)	Percentage of time above range; amount of time (hours and minutes)
Coefficient of variation	Percentage coefficient of variation intraday (ie, within 24 h) and interday (ie, over multiple days)
SD of mean glucose	SD
Mean sensor glucose	mg/dL (mmol/L)
Secondary endpoints (continuous outcomes)	
Time in tight range 70–140 mg/dL (3·9–7·8 mmol/L)	Percentage of time in tight range; amount of time (hours and minutes)
Change in Glucose Management Indicator	Absolute mean change in mmol/mol or percentage
Extended hypoglycaemic event rate <70 mg/dL (<3·9 mmol/L)	Number of events with sensor glucose <70 mg/dL (<3·9 mmol/L) lasting at least 120 min; event ends when glucose returns to ≥70 mg/dL (≥3·9 mmol/L) for ≥15 min
Extended hyperglycaemic event rate >250 mg/dL (>13·9 mmol/L)	Number of events with sensor glucose >250 mg/dL (>13·9 mmol/L) lasting at least 120 min; event ends when glucose returns to ≤180 mg/dL (≤10·0 mmol/L) for ≥15 min
Secondary endpoints (binary outcomes)	
Proportion of participants with time in range 70–180 mg/dL (3·9–10·0 mmol/L) for >70% of each day	Percentage of participants
Proportion of participants with time in range 70–180 mg/dL (3·9–10·0 mmol/L) with ≥5% points improvement from baseline	Percentage of participants
Proportion of participants with time in range 70–180 mg/dL (3·9–10·0 mmol/L) with ≥10% points improvement from baseline	Percentage of participants
Proportion of participants with time below range <70 mg/dL (<3·9 mmol/L) for <4% of each day	Percentage of participants
Proportion of participants with time below range <54 mg/dL (<3·0 mmol/L) for <1% of each day	Percentage of participants
Proportion of participants with time above range >180 mg/dL (>10·0 mmol/L) for <25% of each day	Percentage of participants
Proportion of participants with time above range <250 mg/dL (>13·9 mmol/L) for <5% of each day	Percentage of participants
Composite endpoints	
Proportion with improvement in HbA1c >0·5% points without an in increase in TBR <54 mg/dL (<3·0 mmol/L) of >0·5%	Percentage of participants
Proportion of participants with >10% points improvement in percentage of time in range 70–180 mg/dL (3·0–10·0 mmol/L) without an increase in time below range <54 mg/dL (<3·0 mmol/L) of >0·5%	Percentage of participants
Proportion of participants with mean glucose <154 mg/dL (<8·6 mmol/L) and <1% time below range <54 mg/dL (<3·0 mmol/)	Percentage of participants
Proportion of participants with >70% time in range 70–180 mg/dL (3·0–10·0 mmol/L) and <4% time below range <70 mg/dL (<3·9 mmol/)	Percentage of participants
Proportion of participants with >70% time in range 70–180 mg/dL (3·0–10·0 mmol/L) and <1% time below range <54 mg/dL (<3·0 mmol/)	Percentage of participants

Table 3: Recommended CGM-derived endpoints for clinical trials