REGIONE DEL VENETO
Azienda Ospedale Università Padova

STUDY PROTOCOL (version 2 - 17/09/2024)

Study Title:

The efficacy of different Continuous Glucose Monitoring systems in a cohort of adult patients affected by Inherited Metabolic Disorders prone to Hypoglycemia

Study Type:

Interventional study with CE-marked medical device, single-center, spontaneous

Sponsor:

University Hospital of Padova

Principal Investigator:

Dr. Nicola Vitturi, MD, PhD

Phone: +39 049-8213061

Email: nicola.vitturi@aopd.veneto.it

Coordinating Center:

Division of Metabolic Diseases

Director: Prof. Angelo Avogaro

University Hospital of Padova

Via Giustiniani 2, 35128, Padova, Italy

Abbreviations (examples/alphabetical order)

Abbreviation	Definition
CGM:	continuous glucose monitoring;
CH:	congenital hyperinsulinisms;
FGM:	flash glucose monitoring;
GSD:	glycogen storage disorders;
GV:	glycemic variation;
IMD:	inherited metabolic disorders;
MARD:	mean absolute relative difference;
Rt-CGM:	real time continuous glucose monitoring;
SMBG:	self-monitoring blood glucose;
TAR:	time above range;
TIR:	time in range;
T1DM:	type 1 diabetes mellitus;

Trial Title	The use of Continuous Glucose Monitoring in Inherited Metabolic Disorders prone to Hypoglycemia: Patients' Perspectives and Reliability between Different Devices from an Observational Study
Principal Investigator	Nicola Vitturi
Study Objective/research question	Assessment of perspectives and glycemic reliability of different real time CGM devices in a cohort of adult IMDs patients prone to hypoglycemia
Study Design	Prospective interventional with medical devices CE
Study Population **Major Selection Criteria:**	Adults affected by Glycogen Storage Disorders and Congenital Hyperinsulinism >18 years; Genetic or biochemical diagnosis of Glycogen Storage Disorder or Congenital Hyperinsulinism, in regular clinical follow up at outpatient services.
Estimated total number of subjects	11
Study Duration	First patient in: 01/01/2025 Last patient out: 01/08/2025

Study Background

Inherited metabolic disorders (IMDs) at risk for hypoglycemia include some rare disorders of intermediary metabolism and metabolic cell signaling (1). Among disorders of intermediary metabolism, Glycogen Storage Disorders (GSDs) are the most relevant, while among metabolic cell signaling congenital hyperinsulinism (CH) is the most frequent.

GSDs are a group of monogenic defects in the synthesis or breakdown of glycogen, with prevalent hepatic and/or muscle involvement, as glycogen is particularly abundant in these tissues (2). The overall estimated incidence of GSDs is 1 case per 20,000-43,000 live births, with over 20 types, including subtypes, and a wide spectrum of clinical presentation (2,3). The management of GSDs is based on dietary treatment, with the goal of maintaining glucose homeostasis and preventing long-term complications; organ transplantation may be an option in some patients (2,3). CH is the most frequent cause of persistent hypoglycemia in pediatric patients. In CH, mutations in 12 different key genes cause inappropriate insulin secretion by pancreatic β-cells, resulting in persistent hypoglycemia (4,5). Moreover, suppressing lipogenesis and ketone body formation during hypoglycemia, CH leads to a higher risk of brain injury. Long-term management in CH involves a combination of pharmacologic therapies and, in cases unresponsive to medical treatments, surgical interventions that may include up to subtotal pancreatectomy (removal of 95–98% of the pancreas) (4). Nutritional management includes frequent feeding with high-caloric carbohydrate feeds, UCCS, and sometimes enteral tube feeding (24/24h or only during the night) (5,6).

In IMDs at risk for hypoglycemia subjects have to control their blood glucose levels to evaluate treatment efficacy. Blood glucose check could be performed through self-monitoring blood glucose (SMBG) by finger stick or through continuous monitoring of glucose concentrations in the subcutaneous tissue. In subjects with type 1 diabetes mellitus (T1DM), Continuous Glucose Monitoring (CGM) is considered a primary standard of care, as it has been shown to improve glycemic control and reduce the frequency of hypoglycemia (7,8). CGM avoids the distress and burden of multiple blood capillary measurements per day; it can also detect glycemic patterns and asymptomatic or overnight hypoglycemia by analyzing recorded glucose level data. Trend arrows suggest future glucose patterns and alarms help in preventing hypo and hyperglycemia (9). In patients with T1DM, glycemic targets have been defined for CGM-parameters (i.e., time in range (TIR) and time above (TAR) and below (TBR) range, glucose variability expressed by coefficient of variation (CV)), and the percentage of TIR has been included in the standard set of person-centered outcomes (10,11).

CGM devices have been divided into two classes based on their characteristics: Real-time CGM (Rt-CGM) and intermittent scanned CGM or Flash Glucose Monitoring (FGM). Rt-CGM gives users the possibility to visualize data in real time on a receiver or smartphone app and it is equipped with alarms (threshold, predictive, or related to arrow trend). FGM reports the user's glucose values when the sensor is scanned by a reader or smartphone app. The first FGM version has not been equipped with alarms, while the second version has been equipped with threshold alarms. Then, the latest FGM version of the App can display real time glucose values.

The actual differences in Rt-CGM systems are in costs, possibility to silence the alarms, number of alarms during the day, selection of pre-set targets, possibility of setting additional alerts, time of sensor duration, only use of smartphone or use of specific receiver.

The role and outcomes of CGM in patients with IMDs at risk of hypoglycemia are still debated by researchers and clinicians expert in the field (9,12–14). However, as CGM has been shown valuable in patients with T1DM to detect unrecognized hypoglycemia and monitor individual glycemic variability (GV), its potential benefit for patients with IMDs is high.

The current IMDs guidelines are cautious about the recommendations on the use of CGM and its clinical practice application in nutritional improvements or modifications (15–17). Rossi et al. have recently proposed indications for CGM monitoring and CGM outcome parameters in patients with hepatic GSDs (14). Peeks et al. also indicated outcome parameters for hepatic GSDs (13).

Worth et al. have recently analyzed the state of art of the evidence for the use of CGM in non-diabetic children with hypoglycemia (9). Some suggestions for qualified CGM use have been provided, but a focus on patients' perspectives on the use of different CGM systems is still lacking, especially on recent tools developed by new technologies.

Study Objectives

Primary objective

Assessment of Pre-set targeted time in hypoglycemia and number of episodes of pre-set hypoglycemia during the different periods of use of CGM tools based on different alarms.

Secondary objectives

Accuracy of the two different CGM systems (comparator SBGM by capillary finger stick).

Assessment of patients' perspectives and tolerance to the use of two subsequent different CGM systems and tools, in particular on different types of alarms: Dexcom One Plus (Dexcom) with threshold alarm and Dexcom G7 (Dexcom) with predictive alarm.

Assessment of quality of life and sleep quality.

Assessment and comparison of glycemic control, patients' perspective and tolerance of CGM with USUAL Care CGM.

Study Design

Study Type

Prospective interventional with medical devices CE

Study Site

Sample Size Estimation

11 IMDs at risk for hypoglycemia

The rare condition of disorders investigated needs to be considered for the sample size (e.g. GSD I has a frequency of approximately 1 in 100,000 and the estimated incidence of CHI ranges between 1:27,000 and 1:50,000 live births in outbred western population).

Randomization

Patients will be randomized to start with the use of Dexcom G7 o Dexcom One Plus after baseline.
Methods for randomization: Randomization will be employed to assign participants to different

Continuous Glucose Monitoring (CGM) systems to ensure unbiased comparisons across the study groups. Simple randomization using computer-generated random numbers will be implemented to allocate patients randomly. This method will help distribute confounding variables evenly between groups, thereby minimizing selection bias. Block randomization may also be utilized to maintain balance in the number of participants among the groups throughout the study. Allocation concealment will be maintained until the intervention assignment to prevent any potential influence on patient enrollment.

Statistical method

Definition of Analysis Sets

The following data sets will be analyzed:

- Full analysis set (FAS):
  The set of subjects is as close as possible to the ideal implied by the intention-to-treat principle. All subjects with at least one efficacy follow-up will be included. It is derived from the set of all eligible subjects by minimal and justified elimination of subjects. When handling of missing values of primary outcomes, the last observation carried forward (LOCF) method will be applied.
- Per-protocol analysis set (PPS):
  The per protocol analysis set will consist of all patients in the full analysis set plus the following criteria: completion the treatment process, without any major protocol violations, good compliance (80%~120% medical device and capillary finger sticks compliance) and without missing value in primary outcomes. Patients with at least one major protocol violation (e.g missing the 8 weeks efficacy follow up) will be excluded from the per-protocol analysis.
- Safety Set (SS):
  The safety set will consist of all subjects followed at least one period with one CGM system.

Endpoints:

Primary: number of episodes of pre-set hypoglycemia (hypoglycemia <70 mg/dL and severe hypoglycemia < 54 mg/dL), time above, under or in pre-set target range, glycemic variations during the different periods of use of CGM tools based on different alarms;

Secondary objectives

Secondary: accuracy and MARD (comparator finger capillary sticks) during the use of two different CGM; perspectives and preferences in monitoring and specific use of different alarms with Dexcom One Plus or with Dexcom G7; correlation of primary endpoint with the quality of sleep, quality of life and/or neurocognitive outcomes i.e. attention, assessed by specific questionnaires; perspectives and preferences in monitoring and specific use of different CGM with Usual Care monitoring.

Statistical Analysis (example)

（1） General Principles

Quantitative variable will be described by the total number of cases, number of missing values, mean, and standard deviation, minimum, maximum and median. Categorical variables will be described by the number of cases and percentages.

All statistical tests will be performed using two-sided test, P value less than or equal to 0.05 will be considered to have examined the difference statistically significant (Unless otherwise noted). For comparison between two groups of the general condition, the suitable method shall be adopted to conduct analysis according to the type of indicators; for the comparison among groups of quantitative data, group t test (homogeneity of variance, normal distribution) or Wilcoxon rank-sum test will be adopted according to the data distribution (the Shapiro-Wilk test will be used beforehand to check whether the variables follow a normal distribution or not); for categorical data, the chi-square test or Fisher's exact test (if the chi-square test is not applicable) shall be adopted; for ordered data, Wilcoxon rank-sum test or Cochran-Mantel-Hansel test shall be adopted. Multiple regression analyses will also be considered, including linear regression for continuous dependent variables, Poisson regression and cumulative logit logistic regression for ordered response variables (or logistic regression for dichotomous variables, such as presence/absence). Moreover, ANOVA or mixed-effects models will be used to compare how the effect of interest varies over time within the same subject, repeated measures.

（2） Completion and Baseline Parameters

The summary of the study completion includes the count of competed cases of each study center, the list of dropout cases, the analysis set description, the comparison of dropout rates of the groups and the list of reasons for incompleteness. The summary of baseline parameters includes demographic characteristics (gender, age, height, vital signs etc.), history of illness and medications, and specific Questionnaires about CGM tolerance, perspectives and expectations. Comparisons among the two different CGM devices groups and gold standard by capillary finger stick will be conducted to evaluate MARD and reliability during the period of observation.

（3） Compliance

- Compliance of study: study compliance to the CGM two medical devices and capillary finger sticks of all groups will be described and compared. A list of subjects with poor compliance (80% below or 120% above compliance) will be generated.

Observation parameters list (CRF)

Patients at screening, baseline, after 30 days of **unblinded** *monitoring* with Dexcom G7 and 30 days of **unblinded** *monitoring* with Dexcom One Plus (Fig. 2). The start of the single CGM tool will be randomized (i.e. 50% of patients will random start with G7 and then switch to Dexcom One Plus, and *viceversa*).

1) SCREENING _ General data collection: age, gender, height, body weight, minority, career, income, degree of education, family history, smoking habit, primary diseases or accompanied diseases.
2) SCREENING _ Previous glucose monitoring (referring to the last 8 weeks): number of capillary fingers sticks per day, use (or not) of CGM and type of CGM device
3) SCREENING _ Major comorbidities
4) SCREENING _ Document intake of medications
5) SCREENING _ Adverse events and the rate of hospitalization during the last year
6) BASELINE _ Quality of Life (SF-12 rating scale)
7) BASELINE _ Quality of Sleep (Pittsburgh sleep quality index (PSQI))
8) FOLLOW UP_ Capillary finger sticks glucose values (3 per day) by diary record

9) FOLLOW UP_ CGM values: time above, under or in the pre-set target, number of episodes of pre-set hypoglycemia
10) FOLLOW UP_ CGM tolerance, perspectives and expectations (Specific questionnaires)
11) FOLLOW UP_ CGM Quality of Sleep (Pittsburgh sleep quality index (PSQI), quality of life (SF12)
12) FOLLOW-UP _ Education on the use of CGM device (sensor, receiver or other tools)

Flowchart indicating which parameter is measured when:

Observation Parameters	Screening	Enrollment/Baseline	Follow up - After 30 days	Final Visit study - After 30 days
Informed consent	x			
Demographic (Age, Gender, Career, Degree of Education, Income)	x			
Height	x			
Body Weight	x	x	x	x
Family History	x			
Smoking Habit	x			
Physical exam	x			
Vital signs	x			
Primary Diseases or Accompanied Diseases	x			
Major IMD Comorbidities	x			
Glucometer values		x	x	x
Use of CGM	x			
Documented Intake of Medications	x			
Rate of Hospitalization During the Last Year	x			
Type of CGM Device	x	x	x	x
Capillary finger sticks glucose values (3 per day)		x	x	x
CGM values (time in pre-set hypoglycemia, number of pre-set hypoglycemia, MARD)		x	x	x
Quality of Life Evaluation: SF-12 Rating Scale		x	x	x
Specific Questionnaires for CGM Tolerance, Perspectives, and Expectations		x	x	x
Quality of Sleep: Pittsburgh Sleep Quality Index (PSQI)		x	x	x
Education on the use of CGM device		x	x	x

Observation Parameters	Screening	Enrollment/Baseline	Follow up - After 30 days	Final Visit study - After 30 days
(sensor, receiver, or other tools)				

Study Duration

This study is planned to be initiated in January 2025 (first patient in) and ended in July 2025 (last patient out).

Schematic Study Plan

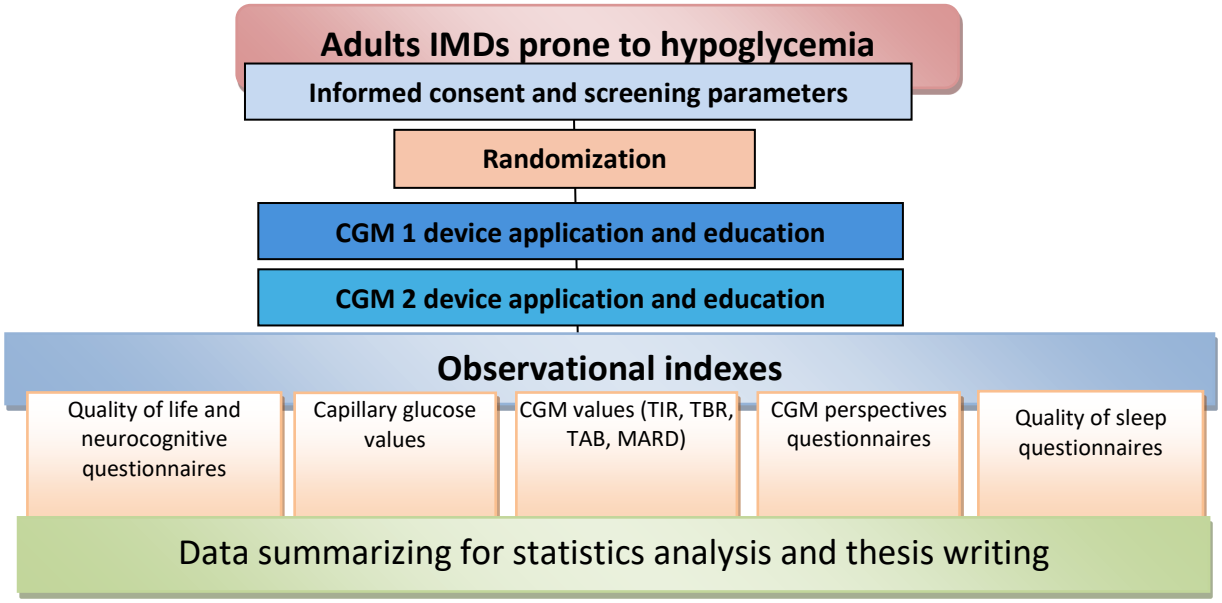

Figure 1. Observational parameters plan

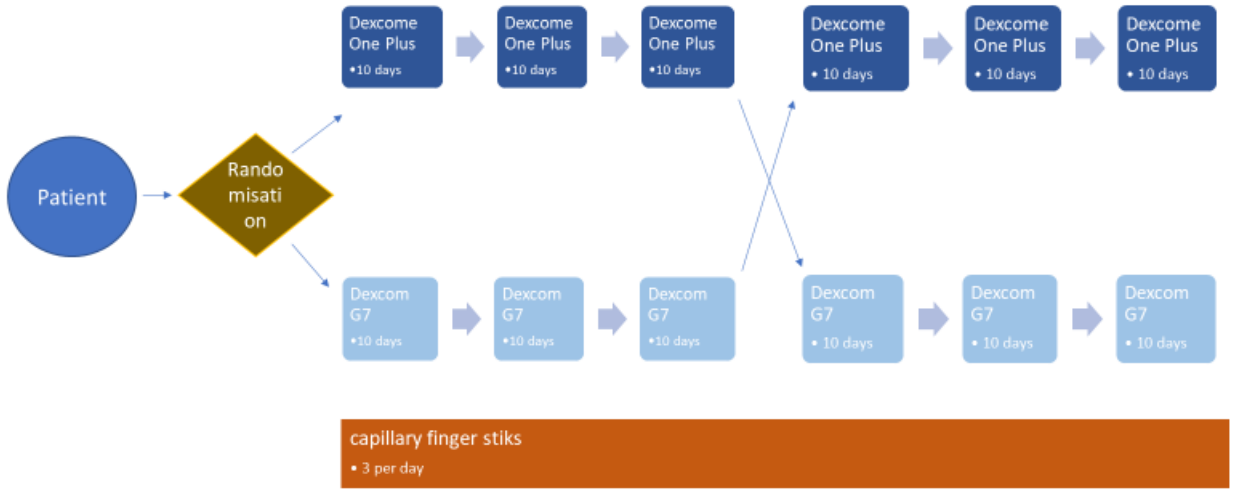

Figure 2. Time design of the study (arrows correspond to a sensor change or a device/system switch)

Study Population

Inclusion Criteria

Adult patients with Glycogen Storage Disease (GSD) or Congenital Hyperinsulinism (CH), aged over 18 years, who have had at least one clinical and biochemical follow-up at the hospital outpatient service within the last year or two years. This includes patients with a biochemical or genetic diagnosis of GSD or CH.

Exclusion Criteria

Inability to sign consent or comply with study procedures. No additional conditions are expected that could introduce bias in the results and therefore require further exclusion criteria.

Study Evaluation

The Ethics Committee of every study site will guarantee the safety of the subjects, receive the effective data and conduct the review on process analysis, and ensure that this study is conducted as per the highest standard of ethics.

Study Quality Control

This study will be conducted by trained and qualified investigators. The investigators shall fill in the CRF in a trustful, detailed and earnest manner to ensure that the content included in the CRF is complete, authentic and reliable. During the study process, the study institution shall conduct examination against case report forms randomly.

Requirements of Ethics

This study complies with the Declaration of Helsinki (version 2000) strictly, and will be conducted as per the relevant medical research regulations and provisions in Italian country.

Before the subjects are included in this study, the investigators are responsible for introducing the purposes, procedures and potential risks of this study to the subjects and their guardians in a complete and comprehensive manner in writing. The subjects have the right to withdraw from this study at any time. Prior to the commencement, it is essential to receive the written informed consent of each subject, which shall be reserved for filing as a clinical research document.

Management Principles

Resume

The latest resume of each investigator and collaborator shall be submitted to the study institution prior to the commencement of this study.

Record Storage in the Study Site

The investigators must preserve all study records, subject-related materials and materials from other sources within the longest period permitted by the hospital. It is recommended that the investigators preserve the study-related materials for 15 years upon conclusion or termination of clinical study.

Protocol Revision

The investigators are prohibited from altering or violating the study protocol at their own discretions. It is approved for implementing the protocol amendment only after discussion and obtaining a written approval or an opinion that such revision is beneficial with signature from the Ethics Committee, unless such revision is necessary to eliminate the danger of patients or only refers to the problems in logic or study management. Any amendment with approval shall be recorded and preserved together with the clinical study protocol after being signed by the investigator and the sponsor.

Any amendment of the clinical study protocol, prior to its implementation, shall have the signature of approval or a signed opinion indicating benefits from Ethics Committee, unless there have the potentials of important safety problems. Under certain circumstances, a revision may be accompanied with the change of the informed consent form. Before implementing the amendment, the investigators must obtain the opinion on the revised informed consent from the Ethics Committee.

Termination of Study Protocol

This study shall be terminated in case of one of the following events:

(1) The study process violates the protocol substantially;
(2) According to new studies' evidence, the continuous implementation of this study may endanger the safety of the subjects;
(3) This study is required to be terminated by health authorities;
(4) The time to recruit the subjects is far longer than the expected one;
(5) The principal investigator determines to terminate this study due to safety problems.

If this study must be terminated, the investigators shall make corresponding decisions and inform the Ethics Committee of the results.

References

1. Ferreira CR, Rahman S, Keller M, Zschocke J, Abdenur J, Ali H, Artuch R, Ballabio A, Barshop B, Baumgartner M, et al. An international classification of inherited metabolic disorders (ICIMD). J Inherit Metab Dis 2021;44:164–77.
2. Hannah WB, Derks TGJ, Drumm ML, Grünert SC, Kishnani PS, Vissing J. Primer Glycogen storage diseases. [cited 2023 Nov 25]; Available from: https://doi.org/10.1038/s41572-023-00456-z
3. Gümüş E, Özen H. Glycogen storage diseases: An update. World J Gastroenterol [Internet] Baishideng Publishing Group Inc; 2023 [cited 2023 Nov 25];29:3932. Available from: /pmc/articles/PMC10354582/
4. Sims K. Congenital Hyperinsulinism. NeoReviews Neoreviews; 2021;22:e230–40.
5. Demirbilek H, Hussain K. Congenital Hyperinsulinism: Diagnosis and Treatment Update. Journal of clinical research in pediatric endocrinology J Clin Res Pediatr Endocrinol; 2017;9:69–87.
6. Arnoux J-B, Verkarre V, Saint-Martin C, Montravers F, Brassier A, Valayannopoulos V, Brunelle F, Fournet J-C, Robert J-J, Aigrain Y, et al. Congenital hyperinsulinism: current trends in diagnosis and therapy.
7. Beck RW, Weinzimer S, Miller K, Beck R, Xing D, Fiallo-Scharer R, Gilliam LK, Kollman C, Laffel L, Mauras N, et al. Effectiveness of continuous glucose monitoring in a clinical care environment: evidence from the Juvenile Diabetes Research Foundation continuous glucose monitoring (JDRF-CGM) trial. Diabetes Care [Internet] Diabetes Care; 2010 [cited 2023 Nov 28];33:17–22. Available from: https://pubmed.ncbi.nlm.nih.gov/19837791/
8. Elsayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, Collins BS, Hilliard ME, Isaacs D, Johnson EL, et al. 7. Diabetes Technology: Standards of Care in Diabetes—2023. Diabetes Care [Internet]

American Diabetes Association; 2023 [cited 2023 Nov 28];46:S111–27. Available from: https://dx.doi.org/10.2337/dc23-S007
9. Worth C, Hoskyns L, Salomon-Estebanez M, Nutter PW, Harper S, Derks TGJ, Beardsall K, Banerjee I. Continuous glucose monitoring for children with hypoglycaemia: Evidence in 2023. Front Endocrinol (Lausanne) [Internet] Front Endocrinol (Lausanne); 2023 [cited 2023 Nov 27];14. Available from: https://pubmed.ncbi.nlm.nih.gov/36755920/
10. Nano J, Carinci F, Okunade O, Whittaker S, Walbaum M, Barnard-Kelly K, Barthelmes D, Benson T, Calderon-Margalit R, Dennaoui J, et al. A standard set of person-centred outcomes for diabetes mellitus: results of an international and unified approach. Diabet Med [Internet] Diabet Med; 2020 [cited 2023 Nov 28];37:2009–18. Available from: https://pubmed.ncbi.nlm.nih.gov/32124488/
11. Battelino T, Danne T, Bergenstal RM, Amiel SA, Beck R, Biester T, Bosi E, Buckingham BA, Cefalu WT, Close KL, et al. Clinical Targets for Continuous Glucose Monitoring Data Interpretation: Recommendations From the International Consensus on Time in Range. Diabetes Care [Internet] Diabetes Care; 2019 [cited 2023 Nov 28];42:1593–603. Available from: https://pubmed.ncbi.nlm.nih.gov/31177185/
12. Worth C, Dunne M, Ghosh A, Harper S, Banerjee I. Continuous glucose monitoring for hypoglycaemia in children: Perspectives in 2020. Pediatr Diabetes [Internet] Pediatr Diabetes; 2020 [cited 2023 Nov 27];21:697–706. Available from: https://pubmed.ncbi.nlm.nih.gov/32315515/
13. Peeks F, Hoogeveen IJ, Feldbrugge RL, Burghard R, de Boer F, Fokkert-Wilts MJ, van der Klauw MM, Oosterveer MH, Derks TGJ. A retrospective in-depth analysis of continuous glucose monitoring datasets for patients with hepatic glycogen storage disease: Recommended outcome parameters for glucose management. J Inherit Metab Dis [Internet] J Inherit Metab Dis; 2021 [cited 2023 Oct 6];44:1136–50. Available from: https://pubmed.ncbi.nlm.nih.gov/33834518/
14. Rossi A, Venema A, Haarsma P, Feldbrugge L, Burghard R, Rodriguez-Buritica D, Parenti G, Oosterveer MH, Derks TGJ. A Prospective Study on Continuous Glucose Monitoring in Glycogen Storage Disease Type Ia: Toward Glycemic Targets. J Clin Endocrinol Metab [Internet] J Clin Endocrinol Metab; 2022 [cited 2023 Oct 11];107:E3612–23. Available from: https://pubmed.ncbi.nlm.nih.gov/35786777/
15. Kishnani PS, Austin SL, Abdenur JE, Arn P, Bali DS, Boney A, Chung WK, Dagli AI, Dale D, Koeberl D, et al. Diagnosis and management of glycogen storage disease type I: A practice guideline of the American College of Medical Genetics and Genomics. Genetics in Medicine Nature Publishing Group; 2014;16:1–29.
16. Kishnani PS, Goldstein J, Austin SL, Arn P, Bachrach B, Bali DS, Chung WK, El-Gharbawy A, Brown LM, Kahler S, et al. Diagnosis and management of glycogen storage diseases type VI and IX: a clinical practice resource of the American College of Medical Genetics and Genomics (ACMG). Genet Med [Internet] Genet Med; 2019 [cited 2023 Dec 8];21:772–89. Available from: https://pubmed.ncbi.nlm.nih.gov/30659246/
17. Koch RL, Soler-Alfonso C, Kiely BT, Asai A, Smith AL, Bali DS, Kang PB, Landstrom AP, Akman HO, Burrow TA, et al. Diagnosis and management of glycogen storage disease type IV, including adult polyglucosan body disease: A clinical practice resource. Mol Genet Metab [Internet] Mol Genet Metab; 2023 [cited 2023 Dec 8];138. Available from: https://pubmed.ncbi.nlm.nih.gov/36796138/