CONTINUOUS GLUCOSE MONITORING IN CRITICALLY ILL PATIENTS: A RANDOMIZED CONTROLLED TRIAL IN THE INTENSIVE CARE UNITS OF HOSPITAL CLÍNIC OF BARCELONA

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1 General Information

1.1 Identification of the Study

Title: **CONTINUOUS GLUCOSE MONITORING IN CRITICALLY ILL PATIENTS: A RANDOMIZED CONTROLLED TRIAL IN THE INTENSIVE CARE UNITS OF HOSPITAL CLÍNIC OF BARCELONA**
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1.2 Identification of the Sponsor/Principal Investigator

Marc Pañero Moreno.

1.4 Identification of the Principal Investigator of the participating centers

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2 Justification

Hyperglycemia is a prevalent condition (75%) in patients in Intensive Care Units (ICUs), as these patients often experience insulin resistance, stress-induced hyperglycemia due to counterregulatory hormones, the use of medications with hyperglycemic effects, or the need for parenteral nutrition, all of which worsen patient safety, morbidity, and mortality. [1–4]

The latest guidelines recommend that in the ICU, the target for glycemic control should be maintained within a range of 140 to 180 mg/dl, or in cases of cardiac surgery or sepsis, within a range of 110 to 140 mg/dl, without inducing episodes of hypoglycemia. [5–7] Currently, the gold standard for glucose monitoring in the ICU is capillary glucose at the bedside or point-of-care (POC) testing. Critically ill patients may require 3 to 6 POC tests per day, and if they require continuous intravenous (IV) insulin infusion, they may need POC testing every hour or even every 15-30 minutes. [6]

Glucose control technology has advanced significantly in recent years, allowing for continuous glucose monitoring (CGM). CGM provides frequent measurements of interstitial glucose levels and glucose trends. However, it's use is not yet validated as the gold standard in the hospital, it's considered standard of care for some outpatient population.

The use of CGM systems offers the opportunity for remote patient monitoring, providing alerts for abnormal values and the opportunity for preventive measures, especially in hypoglycemia prevention. [8] CGM, when used with trained personnel and an established protocol, is feasible, accurate, safe, and has the potential to reduce nursing workload and improve glucose control. [9, 10]

Although most of the analyzed articles demonstrate the feasibility of CGM use in the ICU, they emphasize the need for adequate protocols and safeguards for CGM use in critically ill patients, as well as the need for new randomized controlled trials to validate and demonstrate the benefits of glucose control. [1, 8, 9, 11, 12]

Based on the evidence, there is a justified need to conduct a randomized controlled trial that focuses on demonstrating the benefits of glucose control, reduction in POC testing frequency, and nurses' opinions regarding CGM use in the ICU. Therefore, the objective of this study is to compare the use of CGM as a basis for glucose management decisions in critically ill patients versus decisions based on POC glucose values through a randomized controlled trial. [1–15]

Therefore, considering these needs, we pose the following research question: "Do Critically Ill Patients at Risk of Hyperglycemia (RPH) admitted to the ICU of Hospital Clínic of Barcelona, who use CGM as a basis for glucose management decisions, achieve better glucose control compared to Critically Ill Patients at RPH admitted to the ICU of Hospital Clínic of Barcelona using POC glucose as a basis for glucose management decisions?

2.1 Relevant References

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3 Study Hypotheses

- Null Hypothesis: The use of CGM as a basis for glucose management in critically ill patients with Risk of Hyperglycemia (RPH) in the ICU of Hospital Clínic of Barcelona does not have a significant effect on improving glycemic control compared to the use of GC-POC as a basis for glucose management.

- Alternative Hypothesis: The use of CGM as a basis for glucose management in critically ill patients with RPH in the ICU of Hospital Clínic of Barcelona has a significant effect on improving glycemic control compared to the use of GC-POC as a basis for glucose management.

4 Study Objective and Purpose

- Overall Objective: To compare the use of Continuous Glucose Monitoring (CGM) as a basis for glucose management in critically ill patients with Risk of Hyperglycemia (RPH) in the ICU of Hospital Clínic of Barcelona to the use of Capillary Glucose Point-of-Care (GC-POC) as a basis for glucose management.

- Specific Objectives:
    - Evaluate glycemic control in the experimental group (CGM) and the control group (GC-POC) in critically ill patients with RPH in the ICU of Hospital Clínic of Barcelona.
    - Assess the number of GC-POC measurements in the experimental group (CGM) and the control group (GC-POC) in critically ill patients with RPH in the ICU of Hospital Clínic of Barcelona.

- Evaluate morbidity (hyperglycemia, hypoglycemia) in the experimental group (CGM) and the control group (GC-POC) in critically ill patients with RPH in the ICU of Hospital Clínic of Barcelona.
- Assess mortality in the experimental group (CGM) and the control group (GC-POC) in critically ill patients with RPH in the ICU of Hospital Clínic of Barcelona.
- Gather the opinion of nurses regarding the use of CGM in the experimental group.

4.1 Main and Secondary Variables

The data from CGM will be stored in the Dexcom G7 mobile application (Dexcom, San Diego, California) for data analysis of all CGM devices used. These results will be cross-referenced with the clinical records in the SAP program (SAP SE, Walldorf, Germany) at Hospital Clínic of Barcelona, where the GC-POC measurements and clinical information of the participants will be analyzed while ensuring patient anonymity. All data will be analyzed according to the intention-to-treat principle.

Refer to *Table 1*, which presents a table titled "Outcomes" based on the established objectives. It details all the variables, definitions, units of measurement, and methods for obtaining research results, with the aim of evaluating our objectives.

The variables considered will include glucose measurements such as average glucose, various percentiles (25th, 50th, 75th), interquartile range (IQR), glycemic management indicator (GMI), coefficient of variation (CV), mean amplitude of glycemic excursion (MAGE), average glucose at different times of the day, mean of daily differences (MODD), CGM duration, time in range (TIR), time above range (TAR), time below range (TBR), number of GC-POC measurements, maximum and minimum glucose levels, incidence of hyperglycemia and hypoglycemia, mortality, hospital readmissions, etc.

For confounding outcomes, variables such as age, sex, height, weight, body mass index (BMI), history of diabetes, HbA1c, medical history, reason for admission, ventilator support and duration, need for Computerized Tomography (TC) and Magnetic Resonance (MRI), number of adverse events (The adverse effects will be identified, quantified, recorded, and analyzed through *Table 2*. Will it be reported to the Ethics Committee), duration of stay in the ICU and hospital, SOFA and APACHE II scores, as well as hemodynamic support requirements, will be considered.

Other aspects included in the analysis are the survey results from participating nurses who use CGM. The survey will consist of 18 questions rated on a scale of 1 to 5, with 5 being the highest score and 1 being the lowest. The questions will be related to satisfaction, speed, and safety, adapted to each level assigned by the number, enabling statistical analysis and graphical representation. (See Table 3)

All this information will be represented in contingency tables and graphs for the epidemiological analysis of the participating population, as well as for comparison between population groups, with the aim of demonstrating significant differences between the two established groups regarding the specific variables proposed.

TABLE 1: OUTCOMES ACCORDING TO ESTABLISHED OBJECTIVES				
GENERAL OBJECTIVE				
"Outcomes" Primary	**Definition**	**Type**	**Tool of Measure**	**Unit of Measure**
Glycemia Mean ($\bar{x}$)	The arithmetic mean of glucose levels over a specific period of time. It is calculated by adding all values and dividing the result by the number of samples.	Quantitative Continuous and Dependent.	CGM	$\bar{x}$ mg/dl (±SD)
Percentile 50	Measures the value that represents the central tendency, which is located at the 50% mark of the data in a distribution, indicating the median.	Quantitative Continuous and Dependent.	CGM	mg/dl
Time in range (TIR)	It is defined as the % of time during which glucose levels remain within the target range, which is set at 70-180 mg/dl for patients in the ICU and intermediate care in this study. Important to note that clinical guidelines establish a glycemic target of 140-180 mg/dl or 110-140 mg/dl, depending on the type of patient, like what is practiced at the Hospital Clínic of Barcelona. However, these targets are used to calculate the insulin doses to be administered. Glucose levels established for the TIR of 70-180 mg/dl are considered normal in our study population. Optimal >70%.	Quantitative Continuous and Dependent.	CGM	%
Time Above Range (TAR)	It is defined as the % of time that glucose levels remain >180 mg/dl, dl for patients in the ICU and intermediate care in this study. Optimal <30%.	Quantitative Continuous and Dependent.	CGM	%
Time Below Range (TBR)	It is defined as the % of time during which glucose levels remain <70 mg/dl, dl for patients in the ICU and intermediate care in this study. Clinical guidelines establish hypoglycemia as <70 mg/dl, but for our study, a threshold of <70 mg/dl has been set for safety reasons. Optimal <5%.	Quantitative Continuous and Dependent.	CGM	%

Indicator of glucose management (ICG)	Weighted average of glucose levels, which, through a mathematical formula, estimates HbA1c. Optimal between 5% and 7.5%. $\textbf{HbA1c} = \frac{(\bar{x}\ \text{glycemia} + 46{,}7)}{28{,}7}$	Quantitative Continuous and Dependent.	CGM	%
Coefficient of variation (CV)	Standard deviation of the data is a measure of the relative variability of a data set. Optimal <36%. $CV = \frac{\text{DS de } \bar{x}\ \text{glycemia}}{\bar{x}\ \text{glycemia}} x100$	Quantitative Dimensionless and Dependent.	CGM	%
Average amplitude of the glycemic excursion (MAGE)	It measures the variability of glucose over a certain period of time. It is calculated as the average of all the differences between consecutive blood sugars above or below the SD. Optimal <40mg/dl.	Quantitative Continuous and Dependent.	CGM	$\bar{x}$ mg/dl (±SD)
Mean of glycemia in times of the day.	It measures the arithmetic mean of a blood glucose levels at specific times of the day, such as the hours of insulin administration.	Quantitative Continuous and Dependent	CGM	$\bar{x}$ mg/dl (±SD)

Average of daily differences (MODD)	$\bar{x}$ of the differences between glucose values at the same time on consecutive days. As a reference the hours of insulin administration. A value of >60 mg/dl refers unstable blood sugar. This means that, for a data series {x1, x2, x3, ..., xn}. $MODD = \frac{(x2 - x1 + x3 - x2 + x4 - x3 + ... + xn - xn-1)}{(n - 1)}$	Quantitative Continuous and Dependent.	CGM	$\bar{x}$ mg/dl (±SD)
Interquartile range (IQR)	It is a measure of dispersion that indicates the distance between the 25th quartile (Q1) and the 75th quartile (Q3) in data distribution. A wide IQR implies more variability glycemic. $IQR = Q3 - Q1$	Quantitative Continuous and Dependent.	CGM	mg/dl (±SD)
SPECIFIC OBJECTIVE - 1				
"Outcomes" Primary	**Definition**	**Type**	**Tool of Measure**	**Unit of Measure**
Duration time of the CGM	It is defined as the % of time the CGM has been useful over the total time since insertion. Optimum: >80%. Values in %, been X days the 100%. We defined X, like the total days that the CGM has been used for every patient, 10 days will be the maximum.	Quantitative Discrete and Independent.	CGM	**%**
TIR	It is defined as the % of time during which glucose levels remain within the target range, which is set at 70-180 mg/dl for patients in the ICU and intermediate care. Optimal >70%.	Quantitative Continuous and Dependent	CGM	**%**
TAR	It is defined as the % of time that glucose levels remain >180 mg/dl, for patients in the ICU and intermediate care. Optimal <30%.	Quantitative Continuous and Dependent.	CGM	**%**

TBR	It is defined as the % of time during which glucose levels remain <70 mg/dl, for patients in the ICU and intermediate care. Optimal <5%.	Quantitative Continuous and Dependent.	CGM	**%**
Hypoglycemia Duration (DH)	Average time from the detection of hypoglycemia to its resolution. Hypoglycemia for this study it is defined when the CGM indicates a glucose <70mg/dl until the CGM glucose indicate a glucose >70mg/dl.	Quantitative Continuous and Dependent	CGM	x̄ min (±SD)
SPECIFIC OBJECTIVE - 2				
"Outcomes" Primary	**Definition**	**Type**	**Tool of Measure**	**Unit of Measure**
Number of GC-POC	Number of times a patient has a GC-POC during the study time.	Quantitative Discrete and Independent.	GC-POC	nº of GC-POC
Average number of GC-POC/day	It is the average number of times a patient has a GC-POC per day, during the time of the study.	Quantitative Discrete and Independent.	GC-POC	x̄ nº GC-POC /day (±SD)

SPECIFIC OBJECTIVE - 3				
"Outcomes" Primary	**Definition**	**Type**	**Tool of Measure**	**Unit of Measure**
TAR	It is defined as the % of time that glucose levels remain >180 mg/dl, for patients in the ICU and intermediate care. Optimal <30%.	Quantitative Continuous and Dependent	CGM	**%**
Maximum Glycemia (Gmax)	Average of the maximum glucose values that a patient has recorded each day	Quantitative Continuous and Dependent.	CGM	$\bar{x}$ mg/dl (±SD)
Incidence of hyperglycemia (IH)	It is defined as the frequency at which a patient experiences episodes of hyperglycemia (>180mg/dl). $IH = \frac{\text{nº hyperglycemia}}{\text{nº values of glycemia}} x100$	Quantitative Discrete and Independent.	CGM	%
Percentile 75	It measures the value below which 80% of the data in a distribution lies. In this case indicate hyperglycemia.	Quantitative Continuous and Dependent	CGM	mg/dl
TBR	It is defined as the % of time during which glucose levels remain <70 mg/dl, for patients in the ICU and intermediate care. Optimal <5%.	Quantitative Continuous and Dependent	CGM	**%**

Minimum Glycemic (Gmin)	Average of the lowest blood glucose values that a patient has recorded each day.	Quantitative Continuous and Dependent	CGM	$\bar{x}$ mg/dl (±SD)
Incidence of Moderate Hypoglycemia (IHM)	It is defined as the frequency at which a patient experiences episodes of moderate hypoglycemia (<70mg/dl until >70mg/dl with the CGM) $$\textbf{IHM} = \frac{\text{nº moderate hypoglycemia}}{\text{nº values of glycemia}} \times 100$$	Quantitative Discrete and Independent.	CGM	%
Incidence of Severe Hypoglycemia (IHG)	It is defined as the frequency at which a patient experiences episodes of severe hypoglycemia (<54mg/dl until >54mg/dl with the CGM) $$\textbf{IHG} = \frac{\text{nº severe hypoglycemia}}{\text{nº values of glycemia}} \times 100$$	Quantitative Discrete and Independent.	CGM	%
Percentile 25	It measures the value below which 15% of the date in a distribution lies. In this case indicates hypoglycemia.	Quantitative Continuous and Dependent	CGM	mg/dl
SPECIFIC OBJECTIVE - 4				
"Outcomes" Primary	**Definition**	**Type**	**Tool of Measure**	**Unit of Measure**
Dead (M)	It is the result of the loss of the life in the patient, it will be defined at the 90 days of the discharge of the ICU.	Quantitative Dichotomic	SAP	Si o No

Re-Enters to the ICU (RH)	It is the number of times a patient re-enters to the ICU, it will be defined at the 90 days of the discharge of the ICU.	Quantitative Continuous	SAP	nº re-enters
SPECIFIC OBJECTIVE – 5				
"Outcomes" Primary	**Definition**	**Type**	**Tool of Measure**	**Unit of Measure**
Average of the total Answers	It consists of calculating the average score of all answers obtained. The score goes from 5 to 1, with the best score being 5 and the worst being 1.	Quantitative Discrete and Independent.	Survey Results	x̄ answers (±SD)
Average of each Answer	It consists of calculating the average score of all the answers obtained from each question, separately. The score from 5 to 1, with the best score being 5 and the worst being 1.	Quantitative Discrete and Independent.	Survey Results	x̄ answers (±SD)
Proportion of Total Answers	It consists of calculating the proportion of total answers with each value, with the total number of answers. $M = \frac{\text{nº answers } 5/4/3/2/1}{\text{nº total answers}} x100$	Quantitative Discrete and Independent.	Survey Results	%
Proportion of Answers	It consists of calculating the proportion of each answer with each value, with the total number of participants. $M = \frac{\text{nº answers } 5/4/3/2/1}{\text{nº of participants}} x100$	Quantitative Discrete and Independent.	Survey Results	%

OTHER OUTCOMES OF INTEREST				
"Outcomes" Primary	**Definition**	**Type**	**Tool of Measure**	**Unit of Measure**
Age	Age of the patient.	Quantitative Continuous and Independent	SAP	years
Sex	Sex of the patient, in the case of needing the use of gender, will be considered.	Quantitative Dichotomic and Independent.	SAP	Masculine or Feminine
Height	Patient height.	Quantitative Continuous and Independent	SAP	meters
Weight	Patient weight.	Quantitative Continuous and Independent	SAP	kg
IMC	Body mass index of the patient, calculated as the weight in kilograms divided by the height in meters squared.	Quantitative Continuous and Independent	SAP	kg/m^2
Background of diabetes	Whether or not the patient has history and type of diabetes.	Quantitative Dichotomic and Independent.	SAP	Yes or Not DM1 or DM2

HbA1c	The level of HbA1c in the blood, a measure of the average blood sugar for the three months.	Quantitative Continuous and Independent	SAP	%
$\bar{x}$ Insulin Administrated	It consists of calculating the average insulin administered per day during the use of the CGM in the control and experimental group.	Quantitative Continuous and Independent	SAP	Insulin Units
Pathological History	Other medical history that could be relevant such as hypertension, lung diseases, etc.	Qualitative, Nominal, and Independent.	SAP	-
Performing TC o RM	Annotation of the date and time when the person has undergone TC during the use of CGM to assess its effects on monitoring. The MRI will exclude the patient from the study, but the CGM data will be used until the MRI or removal of the CGM. If the patient continues to meet the study's inclusion criteria, a new CGM will be placed.	Qualitative, Nominal, and Independent.	SAP	-
Reason for Admission	The reason for which the patient has been admitted to the intensive care unit.	Qualitative, Nominal, and Independent.	SAP	-
Ventilator Support	Whether the patient requires ventilator support to assist with breathing. Orotracheal Intubation (OTI), Tracheostomy (TQT), Non-Invasive Mechanical Ventilation (NIMV), High Flow Nasal Cannula (HFNC), or Nitric Oxide (NO)."	Qualitative, Nominal, and Independent.	SAP	IOT, TQT, VMNI, LAF, NO
Duration of Ventilator Support	Duration of ventilator support required by the patient for respiratory assistance.	Quantitative Continuous and Independent	SAP	Hours
Number of Adverse Events	The number of adverse events experienced by the patient during their stay in the intensive care unit. The adverse effects will be identified, quantified, recorded, and analyzed through *Table 2*. Will it be reported to the Ethics Committee.	Quantitative Discrete and Independent.	SAP	nº Adverse Effects

Length of Stay in ICU	The duration of the patient's stay in the intensive care unit.	Quantitative Continuous and Independent	SAP	days
Length of Stay in the Hospital	The duration of the patient's stay in the hospital.	Quantitative Continuous and Independent	SAP	days
SOFA	Sequential Organ Failure Assessment (SOFA) Score: A scale that assesses the severity of organ dysfunction in ICU patients. It is based on six different organ systems. The total SOFA score is the sum of the points from each system and ranges from 0 to 24, where a higher score indicates greater severity."	Quantitative Discrete and Independent.	SAP	0 to 24
APACHE II	Acute Physiology and Chronic Health Evaluation II (APACHE II) System: A scale to assess illness severity and risk of mortality. It measures 12 variables. The total APACHE II score can range from 0 to 71, with a higher score indicating greater risk."	Quantitative Discrete and Independent.	SAP	0 to 71
Hemodynamic Support	Vasoactive drugs, renal replacement therapy, glucocorticoids, blood transfusion, antibiotics, extracorporeal membrane oxygenation (ECMO), etc. All the therapies will include a date and time of initialization and finalization, and ass for the medication, will analyze the time and day of administration.	Qualitative, Nominal, and Independent.	SAP	-
Mean Absolute Relative Difference (MARD)	Accuracy of CGM calculated as the mean absolute relative difference between paired CGM and point-of-care glucose measurements, expressed as a percentage.	Quantitative, Continuous, Dependent	DTS Program Available in: https://www.diabetestechnology.org/dtseg/	%
DTS Error Grid and Clarke Error Grid	Clinical accuracy and risk assessment of CGM compared with paired point-of-care glucose measurements. Results will be evaluated using both the Clarke Error Grid and the Diabetes Technology Society (DTS) Surveillance Error Grid, reporting the proportion of paired values within each risk category.	Quantitative, Ordinal, Dependent	DTS Program Available in: https://www.diabetestechnology.org/dtseg/	%

TABLE 2: ADVERSE EFFECTS RECORD					
TRIAL REGISTRATION NUMBER					
MEDICAL RECORD NUMBER (Will only be identified in the case of reporting to the Ethics Committee and to carry out the appropriate actions)					
CONTROL OR EXPERIMENTAL GROUP					
IDENTIFICATION	Personal Experience	Observation	Third Parties		
OBSERVED ADVERSE EFFECTS					
CONCLUSION	Recovered	In Recovery	No Recovered	Mortal	Others:
OBSERVATIONS					

TABLE 3: SATISFACTION SURVEY OF NURSES TOWARDS CONTINUOUS GLUCOSE MONITORING (CGM)					
Question	**Very Satisfied (5)**	**Satisfied (4)**	**Neutral (3)**	**Dissatisfied (2)**	**Very Dissatisfied (1)**
1. What is the level of satisfaction with the use of CGM in the care of critical patients in the ICU?					
	Very Easy	**Easy**	**Neutral**	**Difficult**	**Very Difficult**
2. How easy to use did you find the CGM in caring for patients in the ICU?					
3. How easy to insert did you find the CGM in caring for patients in the ICU?					
4. How easy did you find the CGM's connection with the receiver?					
	<2 min	**2-5min**	**5min**	**5-10min**	**>10min**
5. How long did it take to insert the CGM?					
6. How long did it take to connect the CGM to the receiver?					
	Very Positive	**Positive**	**Neutral**	**Negative**	**Very Negative**
7. How do you consider the CGM has influenced glycemic control in critical patients in the ICU?					

8. How do you consider the CGM has influenced the nursing workload in the ICU?					
9. How do you consider that the CGM has influenced clinical decision-making in ICU?					
	Very Positive	**Positive**	**Neutral**	**Negative**	**Very Negative**
10. How do you consider the CGM has influenced patient safety in the ICU?					
11. How do you consider the CGM has been accurate in glucose measurements in ICU?					
12. How do you consider the CGM has influenced the speed of glucose measurement in the ICU?					
13. How do you consider the CGM has influenced the detection of hypoglycemia and/or hyperglycemia in ICU?					
14. How do you consider the predictions (trend arrows) of the CGM have been useful in the ICU?					
15. How do you consider it has facilitated control in the case of patients with continuous intravenous insulin infusion in ICU?					

	Yes	Neutral	No
16. Have the CGM predictions helped you adjust insulin doses more appropriately (advance, increase, or decrease the bolus)?			

	Yes	Neutral	No
17. Would you recommend the use of CGM in the care of critical patients in the ICU?			
18. What suggestions or recommendations do you have to improve the use of CGM in the care of critical patients in the ICU?			

5 Study Design

To address the research question, an experimental, prospective, controlled, and randomized clinical trial has been designed, conducted at a single center (Hospital Clínic of Barcelona). The participants will undergo a single-blinded masking procedure.

The research will be conducted once all necessary approvals from Hospital Clínic of Barcelona, the Ethics Committee, the Doctoral Thesis supervisor are obtained and will inform to the Spanish Agency of Medication and Medical Devices (AEMPS). The study will take place from October 2023 to December 2025, with a recruitment period of approximately two years, which can be extended or shortened as needed.

The sampling method is simple random probabilistic sampling. Patients will be randomly allocated in a 1:1 ratio to either the experimental group (CGM) or the control group (GC-POC), creating two parallel groups for comparison. Randomization will be performed at the bedside by the responsible nurses for eligible patients. A box containing all necessary resources and the study protocol will be provided to the ICUs at Hospital Clínic of Barcelona. Within this box, there will be 370 envelopes, each containing either the term CGM or GC-POC indicating the assigned control or experimental group for the participant.

The established intervention involves comparing two randomly assigned groups:

- Experimental Group: Critically ill patients admitted to the ICU at Hospital Clínic of Barcelona at risk of glycemic instability with CGM as the basis for glucose management.
- Control Group: Critically ill patients admitted to the ICU at Hospital Clínic of Barcelona at risk of glycemic instability with GC-POC as the basis for glucose management.

Both groups will have a Dexcom G7 CGM sensor (Dexcom, San Diego, California) placed. Dexcom G7 is a CE-marked medical device used within its approved indications. The CGM used in the control group will be blinded, meaning that the glucose values will be assessed retrospectively.

The CGM Dexcom G7 will be placed on the upper outer arm or abdomen, as indicated by the manufacturer. In the event of needing a CT scan, the CGM can be used without any issue, following the instructions of the CT personnel. However, in the case of a MRI, the sensor will need to be removed beforehand. The duration of a sensor will be a maximum of 10 days, but it will end when the patient is discharged and/or in the event of the patient's death. If the 10 days of the CGM sensor have been completed, it has been accidentally self-removed, is not functioning properly, or the patient requires an MRI or Diathermy, if the patient continues to meet the inclusion criteria, a new Dexcom G7 sensor will be placed.

In the control group, the GC-POC tests will be performed according to the standard protocol of the Hospital Clínic of Barcelona, and routine interventions for glycemic control will be carried out. In other words, in cases of glycemic decompensation, GC-POC tests will be conducted every 6 hours and/or as per the patient requirements. Based on these values, the treatment with multiple doses of insulin will be determined. If the patient needs IV insulin, GC-POC tests can be conducted every 2 hours, 1 hour, or even every 15 minutes, depending on the stability of blood glucose and the nurse's discretion. Therefore, there will be no intervention that modifies the patients' standard treatment in the ICU. The glucose meter used in the facility is CareSens® Dual (Pascual y Furio Diabetes, Paterna, Valencia).

Pel Regarding the experimental group, once the Dexcom G7 CGM is inserted, it is a CE-marked medical device and will be used within its approved indications. The CGM consists of a subcutaneous sensor with glucose oxidase that detects interstitial glucose concentration and transmits chemical signals every 10 seconds. Each sensor requires a 30-minutes warm-up period. The Dexcom G7 CGM averages these values every 5 min and obtains a total of 288 glucose values over a 24-hour period. It can provide values ranging from 40 to 400 mg/dL.

In the experimental group, once the Dexcom G7 CGM is inserted, it will be connected to a compatible Smartphone (depending on funding or manufacturer's recommendations) via the Dexcom G7 app (Dexcom, San Diego, California) as an external monitor for nurses to access the data. The data will be transferred to the Clarity platform (Dexcom, San Diego, California) for data analysis. The devices and platforms used are validated with the CE certification for use with individuals. The devices and platforms used are validated with the CE certificate for use with people, but they will be used in a different environment, therefore the AEMPS will be informed through the NEOPS platform.

The following alarms will be set:

- Glucose level at 200 mg/dL.
- Glucose level at 80 mg/dL (to prevent glucose values <70mg/dL).
- Urgent Low Soon: predictive alert that notifies if sensor glucose is predicted to be <55mg/dL within 20 minutes.
- Urgent Low: alarm that notifies when sensor glucose is <55mg/dL.

In the experimental group, it should be considered that in the case of values outside the CGM measurement range (40 - 400 mg/dL), blood glucose must be confirmed with a GC-POC reading as a safety criterion. Additionally, it is at the discretion of the healthcare team to perform the necessary GC-POC tests, and the CGM can be calibrated with a GC-POC when deemed necessary.

It should be noted that the comparison of GC-POC and CGM cannot be considered if the GC-POC has been obtained at a moment of rapid glucose change, as indicated by the CGM with trend arrows going from ↘ to ↓↓ in the case of decreasing glucose or from ↗ to ↑↑ in the case of increasing glucose. All nurses will receive training to know when calibration is appropriate. Calibration can only be done when the patient's glucose is stable, there is no active insulin administration, it has been more than 3 hours since the last administration, and there are no trend arrows on the sensor. In other words, if these considerations are met, and a GC-POC reading does not match the CGM, calibration can be performed.

The opinions of the nurses in the ICUs at Hospital Clínic of Barcelona will be considered to assess safety criteria, incidents, adverse effects, or issues that may arise during the research. A survey will also be conducted to evaluate these criteria. The survey will be conducted on the formem.clinic.cat platform.

To assess morbidity and mortality, the medical records of the participants will be reviewed at one month, six months, and one year after their participation in the clinical trial.

The critical care nurses at the Hospital Clínic de Barcelona will receive training on CGM at the hospital, including how to insert and configure the sensor before starting the trial. They will also be trained on relevant aspects of conducting the study and considerations regarding patientsafety and anonymity. The training will be conducted at formem.clinic.cat platform.

6 Participant Selection

To carry out the participant selection, inclusion and exclusion criteria have been established (see the next section). The patients will be recruited from the ICUs of Hospital Clínic of Barcelona, and they will be selected as they are admitted to the unit and meet the inclusion criteria, with prior informed consent. The selection will be conducted by the nurses responsible for the patient.

6.1 Inclusion criteria for subjects:

- Aged 18 years or older.
- Admission to the ICU.
- Admission to Intermediate Care.
- Blood glucose >180mg/dl.
- Insulin Requirements

6.2 Exclusion criteria for subjects:

- Pregnancy.
- Individuals with contraindications for the use of CGM (skin issues, allergies to adhesives, etc.).
- End-of-life status.

7 Treatment and Study Schedule

The insulin treatment provided to participants will follow the standard protocol used in the ICU of Hospital Clínic of Barcelona. The specific dosage and administration of insulin will be determined by the medical and nursing team based on each patient's individual needs.

During the study, there will be no scheduled visits to the participants unless any issues arise. The data collected during the hospital admission will be used, and the medical records will be consulted for mortality and morbidity assessment until 90 days from the admission.

8 Statistics

8.1 Sample Size

The study will be conducted at Hospital Clínic of Barcelona, a renowned university hospital in Catalonia, founded in 1906. It is in the center of the city of Barcelona, in the district of Eixample. The hospital has over 800 beds and serves a population of over 2 million people in the Barcelona region and its metropolitan area. For this study, Hospital Clínic of Barcelona, as a research center, has 62 ICU beds and 47 Intermediate Care beds, totaling 109 beds. Considering that, according to the center's data, there is one admission per bed every 3 days, we have an annual population of 13,262 individuals. Based on evidence that hyperglycemia in the ICU represents 75% of cases, our target population consists of 9,947 individuals at risk of developing hyperglycemia.

To conduct our research, we calculated the sample size based on the approximate population of ICU patients at Hospital Clínic of Barcelona in one year (13,262 individuals) with a prevalence of 75% (9,947 individuals), a confidence level of 95%, and a margin of error of 5%. The required sample size for our study is **370 individuals, with 185 individuals in the control group and 185 individuals in the experimental group**. Both groups will be enrolled in parallel and randomly as patients are admitted to the ICUs of Hospital Clínic of Barcelona and meet the inclusion and exclusion criteria.

8.2 Statistical Analysis

To demonstrate the significant difference between the two groups regarding the specific variables under consideration, a statistical analysis will be performed. Firstly, the normality of the data will be checked using the Kolmogorov-Smirnov test, and based on the obtained results, the most appropriate statistical tests will be used. For all tests, a significance level of $p < 0.05$ (less than the significance criterion, $\alpha = 0.05$) will be considered, and a confidence level of 95% will be established. All statistical analysis will be conducted using SPSS software version 27.00 (IBM Corp., Armonk, New York).

9 Ethics and Legal Considerations

This study will adhere to the principles of bioethics, including beneficence, non-maleficence, autonomy, and justice. It will be conducted in compliance with the following:

- Declaration of Helsinki (Fortaleza, Brazil, 2013).
- Law 14/2007, of July 3, on Biomedical Research.
- Regulation 2017/745 on medical devices.

Participants and/or their family members will be provided with the opportunity to learn more about the research project and give their consent to participate (in the case of intubated patients, consent from a family member will be included). This will be done through the "Patient Information and Informed Consent Form" in both Spanish and Catalan. The form will include information about the study: the purpose of the project, the activities that will be carried out, possible risks and benefits, and the option for participants to ask questions and clarify any doubts that may arise. This consent will only be valid if given voluntarily.

It is crucial that the information provided to participants is as understandable as possible. We must ensure that individuals have fully understood the transmitted information before giving their consent.

The study will also require approval from the relevant Research Ethics Committee and permission from the institution where the study will be conducted, in this case, the Hospital Clínic of Barcelona.

Finally, Hospital Clínic of Barcelona, with VAT number 0802070C, will be responsible for the processing, communication, and transfer of personal data of all participants, adhering to compliance with Regulation (EU) 2016/679 of the European Parliament and of the Council of April 27, 2016, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and Organic Law 3/2018, of December 5, on the Protection of Personal Data and guarantee of digital rights.

Regarding the treatment with insulin, it will not be modified and will remain the same as the standard practice in the ICU of Hospital Clínic of Barcelona, established by the medical and nursing team according to the patient's needs in each case.

10 Data Management.

Data will be coded by assigning a unique number to each patient, ranging from 001 to 370. Each number will be associated with the patient's medical record number, creating a separate database for the analyzed information. Only the principal investigator, who is responsible for the data, will have access to this information and will maintain the link between each code and the patient's medical record number. In the event of sharing information with third parties, the data will only be transmitted in coded form, preventing any association with individual participants.

The secure storage and transfer of these data will be conducted using OneDrive (Microsoft Corp., Redmond, Washington), integrated within the software system of the Hospital Clínic of Barcelona, and validated by the center's IT team.

When transferring data to a third party, a specific password will be included, known only to the designated person who cannot transfer it to others without permission from the principal investigator.

The data collected for the study will be retained for a minimum of 5 years after its completion. Subsequently, personal information will only be kept by the center for healthcare purposes and for the primary research study, as well as for other scientific research purposes if the patient has provided consent and if permitted by law and applicable ethical requirements.

During the research, the CGM system data will be connected to a Smartphone (considering the most cost-effective and compatible option based on the study start date), connected to the "Wi-Fi" network of the Hospital Clínic of Barcelona, with the assurance of the IT team.

The Dexcom G7 application will be used, where data will be stored in Dexcom's internal cloud, specifically on the Clarity platform. Only the principal investigator will have access to this data from other devices, from which the data will be extracted for analysis. The cloud will be protected by a username and password. The protection of this data will be maintained and not shared, like how Dexcom currently handles data for individuals with Type 1 Diabetes who use this system.

11 Data Treatment and Record Archiving. Data Confidentiality.

The data will be collected for the sole purpose of evaluating the study objectives or potential publications arising from it.

Treatment, communication, and transfer of personal data of all participants will comply with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of individuals regarding the processing of personal data and on the free movement of such data, and Organic Law 3/2018 of 5 December on the protection of personal data and guarantee of digital rights. The legal basis for processing your data is the consent given in this act, in accordance with Article 9 of Regulation (EU) 2016/679.

The data collected for these studies will be identified only by a code, and no information that allows the identification of participants will be included. Only the study physician and authorized collaborators with access to the source data (medical records) will be able to link the data collected in the study to the patient's medical history.

The identity of the participants will not be accessible to anyone other than in cases of medical emergency or legal requirement.

Identified personal information may be accessed by health authorities, the Research Ethics Committee, and authorized personnel appointed by the study sponsor when necessary to verify data and study procedures, always maintaining confidentiality in accordance with current legislation.

Only encoded data, which in no case will contain information that can directly identify the participant (such as name, initials, address, social security number, etc.), will be transferred to third parties and other countries. In the event of such transfer, it will be for the same purpose as described in the study and ensuring confidentiality.

If a transfer of encoded data outside the EU is made to entities related to the participating hospital, service providers, or collaborating researchers, participants' data will be protected by safeguards such as contracts or other mechanisms established by data protection authorities.

As promoters of the project, we commit to processing the data in accordance with Regulation (EU) 2016/679 and, therefore, to maintaining a record of the processing activities we carry out and conducting a risk assessment of the treatments we perform to determine the measures to be applied and how to implement them.

In addition to the rights already provided by previous legislation (access, modification, objection, and cancellation of data, now deleted in the new Regulation), participants can also limit the processing of data collected for the project if they are incorrect, request a copy, or have them transferred to a third party (portability). To exercise these rights, participants should contact the study's principal investigator or the Data Protection Officer of the Hospital Clínic of Barcelona via protecciodades@clinic.cat.

Data cannot be deleted even if a patient withdraws from the study, to ensure the validity of the research and comply with legal obligations and drug authorization requirements.

The investigator and the sponsor are required to retain the data collected for the study for at least 5 years after its completion. Subsequently, personal information will only be retained by the institution for healthcare purposes and by the sponsor for other scientific research purposes if the patient has given consent, and if permitted by law and applicable ethical requirements.

13 Funding

The study is actively seeking funding from both public and private sources. In no case will there be payment to the researchers, although there may be collaborators who receive financial compensation if funding is obtained. The consumable materials for the Dexcom G7 will be provided by the company Dexcom, located in San Diego, California, as well as the mobile devices, if it’s possible.

14 Publication Policy

There is an explicit commitment from the principal investigator to make all study results public, regardless of whether they are positive or negative. The aim is to present them at the Doctoral School of the University of Barcelona, if accepted by the school. A minimum of two original research papers will be published in indexed journals, with the Principal Investigator as the first author. At least one of the articles will be published in a 1st or 2nd quartile journal, and the rest, at most, in the 3rd quartile, according to the Journal Citation Report (JCR) or Scimago Journal Rank (SJR) rankings.

PATIENT INFORMATION SHEET

STUDY TITLE:
CONTINUOUS GLUCOSE MONITORING IN CRITICALLY ILL PATIENTS: A RANDOMIZED CONTROLLED TRIAL IN THE INTENSIVE CARE UNIT OF HOSPITAL CLÍNIC DE BARCELONA

PRINCIPAL INVESTIGATOR:

Marc Pañero Moreno (Intensive Care Unit Nurse, **panero@clinic.cat**)
CENTRO: Hospital Clínic of Barcelona

INTRODUCTION

You are being invited to take part in a research study. Before you decide whether or not to participate, it is important that you understand why the research is being conducted and what it will involve. This study has been reviewed and approved by a Research Ethics Committee in accordance with applicable legislation, including Spanish Biomedical Research Act 14/2007 and Regulation (EU) 2017/745 on Medical Devices.

Our aim is to provide you with clear and sufficient information so that you can make an informed decision about whether you wish to participate. Please read this information sheet carefully. A member of the research team will explain the study to you and answer any questions you may have. You are encouraged to discuss this information with your family, friends, or any other person you consider appropriate before making your decision.

VOLUNTARY PARTICIPATION

Your participation in this study is entirely voluntary. You are free to decide whether or not to take part. If you choose to participate, you may withdraw your consent and discontinue your participation at any time, without giving a reason. Your decision will not affect your medical care, your relationship with your healthcare professionals, or any treatment you receive now or in the future.

GENERAL DESCRIPTION OF THE STUDY



High blood glucose levels (hyperglycaemia) are common among patients admitted to the Intensive Care Unit (ICU) and are associated with an increased risk of complications, as well as higher morbidity and mortality. In recent years, devices have been developed that allow glucose levels to be monitored continuously, 24 hours a day. These devices have significantly improved glucose management in people living with diabetes. The purpose of this research study is to evaluate whether this technology can also improve glucose control in critically ill patients who are at risk of developing hyperglycaemia during their ICU stay.

This research is a randomized, controlled, single-blind clinical trial. In addition, a retrospective analysis of glucose data collected in the control group will be performed to assess the accuracy, reliability, and performance of continuous glucose monitoring (CGM). Participation in the study will last for the duration of your ICU admission and will end when you are discharged from the ICU as part of your usual care.

The study intervention involves the insertion of a small sensor under the skin that continuously measures glucose levels in the interstitial fluid throughout the day and night (see image). The procedure is minimally invasive and similar to the devices commonly used by people with diabetes. Potential risks associated with sensor insertion include irritation or infection at the insertion site and allergic reactions to the adhesive dressing used to secure the device. These adverse effects are uncommon and have been reported only rarely.

Participants will be randomly assigned to one of two study groups in a 1:1 ratio, meaning that each participant has a 50% chance of being allocated to either the experimental group or the control group. Randomization will be performed by the nursing team at the time of ICU admission. A total of 376 participants will be enrolled in the study.

Participants assigned to the control group will wear a continuous glucose monitoring (CGM) sensor; however, the glucose values will be masked and will not be available to the healthcare team in real time. Participants in this group will receive standard care during their ICU stay. If blood glucose levels become unstable, glucose monitoring will be performed according to usual clinical practice using point-of-care blood glucose measurements, typically every 6 hours and/or as clinically indicated. These measurements will be used to guide insulin treatment and other glucose management decisions.

Participants assigned to the experimental group will also wear a CGM sensor. In this group, glucose values will be available in real time and will be used by the healthcare team to guide glucose management and adjust treatments, including insulin therapy when necessary.

Participants are encouraged to inform the research team of any adverse events or changes that may affect glucose management or study procedures. For participants who are unable to communicate because of their critical illness, all relevant clinical information will be obtained from routine medical and nursing records.

BENEFITS AND RISKS OF PARTICIPATING IN THIS STUDY

You may not receive any direct health benefit from participating in this study. However, previous research has shown that continuous glucose monitoring systems can help improve glucose management and facilitate the early detection of high and low glucose levels.

The device used in this study is the **Dexcom G7 Continuous Glucose Monitoring System**, manufactured by Dexcom. This device has received the necessary European regulatory approvals and is commercially available for glucose monitoring.

The risks associated with participation in this study are considered minimal. Possible risks include irritation, infection, bruising, or discomfort at the sensor insertion site, as well as allergic reactions to the adhesive used to secure the device. These events are uncommon and are generally mild when they occur.

Another potential risk is hypoglycaemia (low blood glucose levels), which is also a known risk of standard insulin treatment when insulin is required. The use of continuous glucose monitoring may help detect hypoglycaemia earlier than conventional monitoring methods, allowing healthcare professionals to intervene promptly and reduce the risk of severe hypoglycaemic events.

If any adverse event related to the study device or procedures occurs, appropriate medical care will be provided according to standard clinical practice.

ALTERNATIVE TREATMENTS

The current standard method for glucose monitoring in Intensive Care Units (ICUs) involves point-of-care blood glucose testing, which requires obtaining a small blood sample through a finger-prick test or other clinically indicated blood sampling methods.

If you decide not to participate in this study, or if you are assigned to the control group, you will continue to receive standard care. Your glucose levels will be monitored according to routine clinical practice, and any insulin treatment or other glucose management interventions will be determined by the healthcare team based on your clinical condition.

If you would like additional information about the study or the available treatment options, the investigator will be happy to answer any questions you may have.

CONFIDENTIALITY

Hospital Clínic de Barcelona, with Tax Identification Number (CIF) 0802070C, is the data controller responsible for processing your personal data. The collection, processing, disclosure, and transfer of personal data relating to all study participants will be carried out in accordance with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 (General Data Protection Regulation, GDPR) and Organic Law 3/2018 of 5 December on the Protection of Personal Data and the Guarantee of Digital Rights.

The legal basis for processing your personal data is the consent you provide by agreeing to participate in this study, in accordance with Article 9 of Regulation (EU) 2016/679 (General Data Protection Regulation, GDPR).

The data collected for this study will be recorded using a unique study code. Your name or other directly identifying information will not be included in the study database. Only the study investigator and authorized members of the research team will be able to link this code to your medical records when necessary for the conduct of the study.

Your identity will remain confidential and will not be disclosed to any unauthorized person, except in the event of a medical emergency or when required by law. Authorized representatives of health authorities, the Research Ethics Committee, and personnel authorized by the study sponsor may have access to identifiable information when necessary to verify study data and procedures. All such access will be conducted in accordance with applicable confidentiality and data protection regulations.

Only coded (pseudonymized) data may be shared with third parties or transferred to other countries. These data will not contain information that could directly identify you, such as your name, initials, address, or social security number. Any such sharing or transfer will be carried out solely for purposes related to this research and under conditions that ensure the confidentiality of your information.

If coded data are transferred outside the European Union, including to collaborating institutions, service providers, or researchers working with the study team, appropriate safeguards will be implemented to protect your data. These safeguards may include contractual agreements or other mechanisms approved by data protection authorities.

In accordance with applicable data protection legislation, you have the right to access, correct, restrict, or object to the processing of your personal data. You may also request a copy of your data or ask for the transfer of data you have provided to another party (data portability), where applicable. To exercise these rights, or if you would like further information about how your data are protected, you may contact the Principal Investigator or the Data Protection Officer of Hospital Clínic de Barcelona at: protecciodades@clinic.cat. You also have the right to lodge a complaint with the relevant Data Protection Authority if you believe that your rights have not been adequately protected.

Please note that data already collected before your withdrawal from the study cannot be deleted, as they are necessary to preserve the scientific validity of the research and to comply with legal and regulatory requirements. However, no new data will be collected after you withdraw your consent.

The Investigator and the Sponsor are required to retain study data for at least five years after completion of the study. After this period, personal information will only be retained by the hospital for healthcare purposes and, where permitted by law and approved by applicable ethical requirements, for future scientific research if you have provided consent for such use.

FINANCIAL COMPENSATION

Participation in this study will not involve any costs to you. The study device and all study-related procedures will be provided free of charge. You will not receive any financial compensation for participating in this research.

OTHER RELEVANT INFORMATION

If any new information becomes available during the study that may affect your willingness to continue participating, you will be informed as soon as possible by a member of the research team.

If you decide to withdraw your consent to participate in this study, no new data will be collected from you. You may also request the destruction of any identifiable samples that have been retained, where permitted by applicable legal and regulatory requirements, to prevent their use in future analyses.

You should also be aware that the study investigators may withdraw you from the study if they consider it necessary. This may occur for safety reasons, because of an adverse event related to the study procedures, or if it is considered that study requirements cannot be adequately followed. In all cases, you will be informed of the reason for your withdrawal whenever possible.

By signing the accompanying informed consent form, you agree to participate in the study and to comply with the study procedures that have been explained to you.

When your participation in the study ends, you will continue to receive the best available treatment as determined by your healthcare team. The continuous glucose monitoring device used in this study may not remain available after your participation has ended. Therefore, neither the investigator nor the sponsor is obligated to provide continued access to the study device or procedures once the study has been completed.

Particioant Informed Consent Form

Study Title: "CONTINUOUS GLUCOSE MONITORING IN CRITICALLY ILL PATIENTS: A RANDOMIZED CONTROLLED TRIAL IN THE INTENSIVE CARE UNIT OF HOSPITAL CLÍNIC DE BARCELONA".
Protocol Version and Date: Version 4 of *11th of March of 2024*

I, *(Participant Full Name):*

- I have read the Participant Information Sheet provided to me for this study.
- I have had the opportunity to ask questions about the study.
- I have received sufficient information about the study.
- I have discussed the study with:
- I understand that my participation is voluntary.
- I understand that I may withdraw from the study:
  - At any time.
  - Without giving a reason.
  - Without any effect on my medical care or legal rights.

- In accordance with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 (General Data Protection Regulation, GDPR) and Organic Law 3/2018 of 5 December on the Protection of Personal Data and the Guarantee of Digital Rights, I have been informed about the collection and processing of my personal data, the purpose of such processing, and the recipients of the information.

- I freely agree to participate in this study.

Participant Signature	Investigador Signature
Date:_____/____/_____	Date:/____/____

I wish to be informed of any information arising from this research that may be relevant to my health:

□ YES □ NO

Participant Signature	Investigador Signature
Date:_____/____/_____	Date:_____/____/_____

Legally Authorized Representative Informed Consent Form

(to be used when the participant is unable to provide consent due to critical illness, sedation, or intubation)

Study Title: "CONTINUOUS GLUCOSE MONITORING IN CRITICALLY ILL PATIENTS: A RANDOMIZED CONTROLLED TRIAL IN THE INTENSIVE CARE UNIT OF HOSPITAL CLÍNIC DE BARCELONA".
Protocol Version and Date: Version 4 of *11th of March of 2024*

I, *(Full Name of the Legally Authorized Representative):*

Relationships to the participant (e.g., spouse, partner, parent, child or other): of

(*Participant Full Name*):

- I have read the Participant Information Sheet provided to me for this study.
- I have had the opportunity to ask questions about the study.
- I have received sufficient information about the study.
- I have discussed the study with:
- I understand that my participation is voluntary.
- I understand that I may withdraw from the study:
  - At any time.
  - Without giving a reason.
  - Without any effect on my medical care or legal rights.

- In accordance with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 (General Data Protection Regulation, GDPR) and Organic Law 3/2018 of 5 December on the Protection of Personal Data and the Guarantee of Digital Rights, I have been informed about the collection and processing of my personal data, the purpose of such processing, and the recipients of the information.

- I freely give my consent so that (*Participant Full Name*):

, participate in the study.

Legally Authorized Representative Signature

Date……./……../…….. Signature:

Investigator Signature

Date……./……../……Signature: