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Glycemic control in Type 1 Diabetes Mellitus with the Continuous Glucose Monitoring System compared with the Self Monitoring of Blood Glucose System: a randomized control trial.

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FINAL DEGREE PROJECT

Glycemic control in Type 1 Diabetes Mellitus with the Continuous Glucose Monitoring System compared with the Self Monitoring of Blood Glucose System: a randomized control trial

Medicine Degree

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Delivery: 13/04/2015

Index

1. Abstract 3
2. Introduction 6
3. Hypothesis 9
4. Objectives 10
5. Methodology 11
    - 5.1. Study design 11
    - 5.2. Participants 11
        - 5.2.1. Inclusion and exclusion criteria
        - 5.2.2. Sample
        - 5.2.3. Randomization
    - 5.3. Variables 13
    - 5.4. Measurement instruments 15
    - 5.5. Information collection 16
    - 5.6. Statistical Analysis 18
    - 5.7. Activity Chart 19
6. Ethical aspects and other considerations 22
7. Limitations and strengths 23
8. Expected Outcomes 24
9. Collaborating Team 25
10. Bibliography 26

Annex 28

Acronyms

- Type 1 Diabetes: T1D
- Intensive Insulin Treatment: IIT
- Multiple Daily Injections: MDI
- Subcutaneous Insulin Infusion: SCII
- Neutral Protamine Hadgedorn: NPH
- Self-Monitoring Blood Glucose System: SMBG system
- Continuous Glucose Monitoring System: CGM system
- Glycated Hemoglobin: HbA1c

1. Abstract

Background: Despite the intensive treatment of diabetes some patients usually do not achieve the optimal control levels. Thus, the ambulatory glucose control has acquired a more important role. The most used system is the Self-Monitoring of Blood Glucose. However, nocturnal hypoglycemia and postprandial hyperglycemia may be unnoticed. Because of that, in recent years the Continuous Glucose Monitoring system has been considered as an alternative to the standard method.

Objective: The aim of this study is to demonstrate that the Continuous Glucose Monitoring system presents a higher reduction (0,5-1%) in the glycated hemoglobin than the Self-Monitoring of Blood Glucose system. The secondary objectives include evaluating the relation between glucose control and patients' age and studies level for both methods, and finally we will compare the quality of life achieved with each system.

Participants: Patients with Type 1 Diabetes, from 8 to 35 years old, and more than 18 months of progression, attended in the reference hospitals of the Vallès Occidental.

Methodology: Multicentric randomized controlled trial. The participants will be divided in two groups: the Intervention Group will use the Continuous Glucose Monitoring system and the Control group will use the Self-Monitoring of Blood Glucose system. They will be followed during 13 months. The main independent variable is the system used by each group, and the main dependent variable will be the glycated hemoglobin, which will be measured by a blood analysis every three months. The statistical analysis will be carried out by the T-Student test and the ANOVA test for repeated measures.

Expected Outcomes: We expect to obtain a higher reduction of the glycated hemoglobin in the Continuous Glucose Monitoring system group. According to our hypothesis, optimal glucose control will be achieved in patients older than 25 years old, with the highest degree of education. Finally, we expect to observe better results on quality of life in the Intervention group.

MeSH terms: Type 1 Diabetes, Continuous Glucose Monitoring System, Self Monitoring of Blood Glucose, Intensive Insulin Treatment.

Resum

Introducció: Tot i el tractament intensiu de la diabetis alguns pacients no aconsegueixen un control òptim dels nivells glicèmics. En conseqüència, el control ambulatori de la glucosa ha anat agafat un paper més important. El sistema més utilitzat és el *Self-Monitoring of Blood Glucose.* Tot i així, les hipoglucèmies nocturnes i les hiperglicèmies postprandials poden passar inadvertides. És per això, que en els darrers anys el sistema *Continuous Glucose Monitoring* s'ha anat convertint en una alternativa al sistema estàndard.

Objectius: L'objectiu principal d'aquest estudi es demostrar que el sistema *Continuous Glucose Monitoring* permet una reducció major (0,5-1%) de l'hemoglobina glicosilada que el sistema *Self-Monitoring of Blood Glucose.* Els objectius secundaris inclouen l'avaluació de la relació entre el control glucèmic i l'edat i nivell d'estudis dels pacients. Finalment, també es comparerà el nivell de qualitat de vida que s'obtindrà amb cada mètode.

Participants: Pacients Diabetis Tipus 1, d'entre 8 i 35 anys, i amb més de 18 mesos d'evolució de la malaltia dels hospitals de referència del Vallès Occidental.

Mètodes: Assaig clínic aleatoritzat multicèntric. Els participants seran dividits en dos grups: Grup d'Intervenció que utilitzarà el sistema *Continuous Glucose Monitoring* i el Grup Control que utilitzarà el sistema *Self-Monitoring of Blood Glucose.* Els participants seran seguits durant 13 mesos. La principal variable independent serà el sistema de control utilitzat i la principal variable depenent serà la hemoglobina glicosilada, que serà mesurada mitjançant un anàlisis de sang cada tres mesos. L'anàlisi estadístic es durà a terme mitjançant el test de T-Student i el test de ANOVA per mesures repetides.

Resultats esperats: Esperem obtenir una disminució de l'hemoglobina glicosilada del 0,5-1% major en el grup Intervenció. D'acord amb la nostra hipòtesis, els nivells òptims de control glucèmic seran obtinguts en pacients majors de 25 anys i a major nivell d'estudis. Finalment, també esperem trobar un major nivell de qualitat de vida en els pacients del grup *Continuous Glucose Monitoring.*

Paraules clau: Diabetis tipus 1, Monitorització Contínua de la Glucosa, Automonitorització de la Glucosa en sang, Tractament Intensiu amb Insulina.

Resumen

Introducción: A pesar del tratamiento intensivo de la diabetes, algunos pacientes no consiguen un control óptimo de los niveles glucémicos. En consecuencia, el control ambulatorio de la glucosa ha ido adquiriendo un papel más importante. El sistema más utilizado es el *Self-Mointoring of Blood Glucose.* Sin embargo, las hipoglucemias nocturnas i las hiperglicemias postprandiales puedan pasar inadvertidas. Por eso, en los últimos años el sistema *Continuous Glucose Monitoring* se ha convertido en una alternativa al sistema estándar.

Objetivo: El objetivo principal de este estudio es demostrar que el sistema *Continuous Glucose Monitoring* permite una reducción mayor (0,5-1%) de la hemoglobina glucosilada que el sistema *Self-Monitoring of Blood Glucose.* Los objetivos secundarios incluyen la evaluación de la relación entre el control glucémico i la edad i el nivel de estudios de los pacientes. Finalmente, también se comparará el nivel de cualidad de vida que se obtenga con cada método.

Participantes: Pacientes con Diabetes Tipo 1, de entre 8 i 35 años, i más de 18 meses de evolución de la enfermedad de los hospitales de referencia del Vallès Occidental.

Métodos: Ensayo clínico aleatorizado multicéntrico. Los participantes serán divididos en dos grupos: Grupo de Intervención que utilizarán el sistema *Continuous Glucose Monitoring* i el Grupo Control que utilizarán el sistema *Self-Monitoring of Blood Glucose.* Los participantes serán seguidos durante 13 meses. La principal variable independiente será el sistema de control utilizado y la principal variable dependiente será la hemoglobina glucosilada , la cual será medida mediante un análisis de sangre cada tres meses. El análisis estadístico se llevará a cabo mediante el test de T-Student i el test de medidas repetidas ANOVA.

Resultados esperados: Esperamos obtener una disminución de la hemoglobina glucosilada del 0,5-1% mayor en el grupo Intervención. De acuerdo con nuestra hipótesis, los niveles óptimos de control glucémico se obtendrán en pacientes mayores de 25 años i mayor nivel de estudios. Finalmente, también se esperan encontrar mejores niveles de calidad de vida en los pacientes del grupo *Continuous Glucose Monitoring.*

Palabras clave: Diabetes Tipo 1, Monitorización Continua de la Glucosa, Automonitorización de la Glucosa en sangre, Tratamiento Intensivo con Insulina.

1. Introduction

Type 1 Diabetes Mellitus (DM1) or juvenile diabetes is a chronic metabolic disorder that onsets during childhood or adolescence. It represents nearly 10% of the total Diabetes Mellitus, and each year nearly 250 or 270 new cases are diagnosed in Catalonia in people younger than 30 years old (1). The pathogenic sequence that explains this disorder implies an immune-mediated process in which the beta cells producers of insulin from the islets of Langerhans are destroyed. However, it is not always possible to demonstrate an autoimmune process in all the patients, and some of them will be classified as idiopathic cases. The cause of this disorder has not been well demonstrated yet, but it is thought to be due a complex interaction between environmental, genetic, and immunity factors (2). The loss of these cells requires a chronic treatment based on insulin (3). The metabolic disorder that comes with DM1 produces secondary physiopathological effects on some systems of the organism. Thus, a good metabolic control will minimize the acute (hypoglycemia, hyperglycemia and diabetic ketoacidosis) as well as chronic complications (microvascular and macrovascular) (4).

The treatment for this disease has always been in controversial. The treatment mostly used is the intensive insulin therapy (IIT) (5). The two most debated methods include: 1) Multiple daily injections (MDI), which is based on one dose of long acting insulin offering a 24-hour control, plus a bolus of rapid acting insulin before each meal (6)**;** 2) Continuous subcutaneous insulin infusion (SCII) pumps, which administrates the insulin in a continuous way during 24h with a subcutaneous catheter (7). Some studies have demonstrated that the intensive insulin therapy is more efficient in the glycated hemoglobin control compared to the conventional therapy with NPH (Neutral Protamine Hadgedorn) insulin, which was used before the commercialization of the new insulin analogues (8). However, it is not well demonstrated yet, which of the two administration methods of the intensive insulin therapy is the best. Some research groups consider that the MDI system supposes the most physiological insulin pattern, and a more flexible therapy than the CSII (9). Other groups have demonstrated that the CSII system allows a better glycated hemoglobin control and a better quality of life than the MDI system because of the avoidance of the injections of the MDI system (9,10).

Despite the intensive treatment of diabetes with the most sophisticated systems of SCII, MDI and the different types of insulin available in the market, diabetic patients usually do not achieve the optimal control levels (11). The parameters that can help us determine the good or bad control of the disease include: the glycated hemoglobin measured every 3 or 6 months, the number of hypo or

hyperglycemias that the patients refer, the ambulatory glucose control and the apparition of chronic complications.

During the last years, the ambulatory glucose control has acquired a more important role. During the 80's the system of self-monitoring blood glucose (SMBG) was introduced. This system has evolved up to the point to become the one used the most (12). It consists in an analysis of a drop of blood obtained by puncturing the tip of a finger, and then introducing it in a strip, previously inserted in a glucometer (13). The information obtained allows the patients to take decisions about the dose of insulin, the need to intake more carbohydrates, etc. The new era of the ambulatory control of blood glucose started in the late 90's with the introduction of the first continuous glucose monitoring system (CGM) (14). That works by introducing a sensor through the skin into the subcutaneous tissue in order to have access to the interstitial fluid. The sensor is linked to a transmitter. Each sensor measures the glucose every 5 or 10 seconds, and obtains the mean every 10 minutes, which is stored in the transmitter (6,7). Thus, the patient can obtain the blood glucose level without a puncture, and the glucose curve of the whole day(15) .

Nowadays, the SMBG system is still the method of choice in our country. This fact could be either because it is the cheapest method, or because it is the method with more years of experience, or because it has more devices in the market, or because it has been demonstrated that this system plus an intensive therapy with insulin allows the patient to achieve a good glucose control (16). In any case, this method also has some risks. Besides being an invasive test, it only shows punctual measures. Moreover, just few patients with type 1 DM measure their blood glucose levels after eating or during the night (11). Thus, the nocturnal hypoglycemia and postprandial hyperglycemia may be unnoticed (6,12). Because of that, in recent years the CGM system has been considered as an alternative to the SMBG system for the ambulatory glucose control in T1D patients.

During years, several studies have been carried out to determine which of the two systems for the ambulatory glucose control, allowed the patients to get a better control. Early studies concluded that the CGM system was better than the SMBG system without any significant differences (3,17). Over time, the research conditions and the methodology have become stricter, to finally being able to demonstrate that the CGM system reduced not only the glycated hemoglobin, but also, the time spent in hypoglycemia compared with the SMBG system in adults with DM1 (5,11,15,18). Concurrently, there were studies to find a profile for the ideal patient to take advantage of all the information the CGM system provides compared with the SMBG system; and the conclusion was that the patients that would benefit the most were those with type 1 diabetes, older than 18 years, with no recent onset, and with glycated hemoglobin between 7% and 9% (19).

Some groups have carried out isolated studies on quality of life and the satisfaction index of the patient that each system provides (20).

In Spain, there are no studies in which these two methods are compared. So, the efficacy of these systems applied to our population is limited. The deficiency of data supporting the CGM system may be a reason, as it is not subsidized by the social security in Spain. Moreover, a research including the comparison of glycated hemoglobin, the acute complications, the quality of life of the patient, has never been carried out.

With all this information our hypothesis (H) is: H_1) The CGM system allows a decrease of glycated hemoglobin around 0,5-1% compared with SMBG system. H_2) The CGM system allows a better control of the acute complications (hyperglycemia and hypoglycemia) than the SMBG system. H_3) Type 1 diabetes patients older than 25 years old with secondary studies or more are the ones who would take advantage of the CGM system the most. H_4) It also contributes to improve the quality of life measured by the "Modified Spanish Version of Diabetes Quality of Life Questionnaire (21) compared with the SMBG system.

Under this hypothesis we propose a randomized control trial with the aim (O) to: O_1) To evaluate the efficacy of the CGM system in comparison to the SMBG system by obtaining a decrease of the glycated hemoglobin around 0,5-1%. O_2) To demonstrate that different control is reached depending of the age range in both studied systems, while achieving a better control in 25 year old patients or older. O_3) To study the relation between having a higher degree of education and a better glucose control with the CGM system. O_4) To demonstrate that the CGM system allows a reduction of acute complications compared with the SMBG system. O_5) To study the difference of the quality of life achieved for each system.

2. Hypothesis

1. The CGM system allows a higher reduction (0,5-1%) of the glycated hemoglobin than the SMBG system.
2. The CGM system reduce the acute complications (hyperglycemia and hypoglycemia) in T1D patients
3. Patients older than 25 years old with high studies achieve a better glycemic pattern for both methods than younger patients with no studies.
4. The CGM system improves the quality of life measured by the “Modified Spanish Version of Diabetes Quality of Life Questionnaire” in comparison with the SMBG system.

3. Objectives

1. Main objective:
    - To evaluate the efficacy of the CGM system in comparison to the SMBG system by obtaining a decrease of the glycated hemoglobin around 0,5-1%.
2. Secondary objectives:
    - To demonstrate that different control is reached depending of the age range in both studied systems, while achieving a better control in 25 year old patients or older.
    - To study the relation between having a higher degree of education and a better glucose control with the CGM system.
    - To demonstrate that the CGM system allows a reduction of acute complications compared with the SMBG system.
    - To study the difference of the quality of life achieved for each system. To study the difference of the quality of life achieved for each system.

4. Methodology

Study design

Our study design will consist in a multicentric randomized control trial, with the objective to test the main and secondary hypothesis. Blind technics will not be used on patients due to the impossibility of blinding an invasive technique, which must be controlled, by the patients in an ambulatory way. Moreover, it is expected to obtain better results for both methods if the participants know about the technique used. The study duration will be 28 months.

The participants will be divided in two groups: Intervention group or CGM system (group 1) and Control group or SMBG system (group 2). Group 1 patients will go through an ambulatory glucose control with the CGM system, and should wear a sensor 24 hours a day for 12 months. Group 2 patients will go through an ambulatory glucose control with the SMBG system, and should perform a minimum of 4 controls (before each meal and before going to bed) a day during 12 months.

The study will be composed of 4 periods: (0) Protocol elaboration, (1) Enrollment period, (2) Intervention period, (3) Evaluation period. The enrollment period will take place from month 7 to month 12 of the study. We will go through the selection and training of the participants. In this period, we also will inform the participants about the study characteristics, the voluntary participation and the possibility to step out any time. Finally, an Informed Consent Document will be given to the participants or their tutors, which must be signed to participate in the study. After that, we will go through the intervention period, and prior the randomization process, a baseline evaluation will be carried out in order to obtain the first data of each participant. The intervention period will take thirteen months, during which the participants, who will have been randomly assigned in one of both groups (intervention or control group), will be followed up and studied. The study will finish with the evaluation of the obtained results and it's publication. This period will take three months.

Participants

There are four hospitals located in the Vallès Occidental: Parc Taulí Sabadell, Consorci Sanitari de Terrassa, Hospital Mútua de Terrassa and Hospital General de Catalunya. Among their services, all of them have an endocrinology unit. Attending that all the clinical histories have

information related to age, type of diabetes and time of evolution, we will contact all the endocrinology services, and we will ask them to collaborate with our study providing us with a list of patients aged from 8 to 35 years old, with T1D, and more than 18 months of progression, from their hospital registers.

Using the provided list, we will invite all the patients to participate in our study. During the enrollment period the patients will be screened according to all the other inclusion and exclusion criteria.

Inclusion and exclusion criteria

All the patients that meet the following inclusion criteria will be included in our study:

- Age between 8 and 35 years old (both included).
- Patients diagnosed with Type 1 Diabetes Mellitus.
- The onset of Diabetes for more than 18 months.
- Glycated hemoglobin levels between 7 and 9%.
- Intensive insulin treatment (MDI or SCII).
- Ambulatory glucose control with SMBG system and at least 4 daily controls till the inclusion in the study.

The patients will be excluded if they meet any of the following exclusion criteria:

- Diabetes Mellitus Type 2 diagnose, Diabetes Type MODY, Diabetes type LADA or pregnancy Diabetes.
- Pregnant patients with Type 1 Diabetes.
- Patients with Type 1 Diabetes onset for more than 18 months, who persist in "Honeymoon".
- Patients presenting chronic diabetes complications during the selection process.
- Patients who had previously used the CGM system for the ambulatory glucose control.

Sample

To estimate the sample size, even though not many studies have been published on this method, we will use the study carried out by *"The Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group"* (11) as an example to calculate an approximation of the number of participants needed. The primary outcome will be the change in the mean glycated hemoglobin level from baseline in 12 months. We have used the "Granmo" program to calculate the sample size with the following criteria. We expect the optimal control to be achieved in an 80-90% of the participants from the intervention group, and in 60% of the participants from the control group. We plan to have

a power of 90% within each group to detect a difference between the study groups of 20% (standard deviation of 0.9%). An alpha risk of 0.05, a beta risk of 0.2, and a loss of follow-up of no more than 15%, will be considered for the calculation. Taking into account these criteria we will need 95 patients in each group

To summarize, there will be 190 participants in the study aged between 8 and 35 years old, with T1D, and more than 18 months of evolution, with the aim to evaluate if the CGM system results in a higher reduction of the glycated hemoglobin compared to the SMBG system.

Randomization

After the enrolment period, once the intervention period has started and the baseline evaluation will be done, the randomization process will take place. This process will be carried out by a computer system, according to a predetermined random sequence with a 1:1 ratio.

Variables

Main independent variable:

- **Ambulatory glucose control:** it is a nominal dichotomy qualitative variable. Each study group will use a different system for the ambulatory glucose control, which will represent the intervention of our research. It will be evaluated by the following categories:
    - **Intervention Group – CGM system:** it works by introducing a sensor through the skin into the subcutaneous tissue, which measures the glucose every 5 or 10 seconds, and obtains the mean every 10 minutes. The result obtained through a transmitter give the patient information about the punctual measure, and the curve of all measures average.
    - **Control Group – SMBG system:** It consists in an analysis of a drop of blood obtained by puncturing. The result obtained, represents the blood glucose level in this punctual moment.

Main dependent variable:

- **Glycated hemoglobin (HbA1c):** It is a continuous quantitative variable expressed by a percentage. It is an hemoglobin fraction formed from the interaction between hemoglobin and glucose. HbA1c reflects average glycaemia over 3 months, the average life of erythrocytes. The formation speed is directly proportional to the blood glucose concentration. It has strong predictive value for diabetes complications. Thus, HbA1c testing

should be performed routinely in all patients with diabetes. The frequency of HbA1c testing should depend on the clinical situation and the clinician's judgment. It is recommended to analyze this parameter every 3 or 6 months. The normal value is under 6%. The optimal values in diabetic patients are < 7%. The result interpretation is explained in the **Annex 1.**

Secondary dependent variables:

- **Quality of life:** it is a quantitative discrete variable, which will be collected by the "Modified Spanish Version of Diabetes Quality of Life Questionnaire" **(Annex 3)**. This qquestionnaire is composed of four dimensions: satisfaction, impact, social and vocational concerns, and diabetes related worries. All the points will be summed up obtaining a final score between 0 and 100, whereas 0 means the minimum satisfaction, and 100 the maximum.

- **Acute complications**
    - Hypoglycemia: this is a quantitative discrete variable. It is the most frequent complication related to insulin treatment. It is defined by a capillary glycemic value under 70 mg/dl. However, it is not the most accurate definition in terms of clinical significance, thus hypoglycemic symptoms can be detected with a glycemic capillary value over 70 mg/dl, and an hypoglycemia with values under 70 mg/dl can also be unnoticed. This variable will be registered by patients with the provided diaries, and it will be evaluated by the number of hypoglicemies per week:
    - Hyperglycemia: it will be evaluated as a quantitative discrete variable. Attending to the control objectives, it is standardized that the optimal postprandial glycaemia may be less than 180 mg/dl. Thus, a value above 180 mg/dl, 2 hours after a meal will be considered as an hyperglycemia. This variable will be evaluated by the number of hyperglicemies per week.
    - Diabetic Ketoacidosis: it is a quantitative discrete variable. It is defined by biochemical parameters as:
        - Glycaemia > 250 mg/dl
        - Positive Ketone bodies in urine or blood
        - Metabolic acidosis (pH < 7,30)
        - Elevated anion gap (>10)
        - Decreased plasmatic bicarbonate (< 18 mEq/l)

      The number of episodes per year will evaluate this variable.

Secondary independent variables:

- **Education:** it is an ordinal qualitative variable. It will be divided in the following categories:

    - Primary school
    - Secondary school
    - Graduate studies

- **Age:** it will be considered as an ordinal qualitative variable. It will be divided in the following categories:
    - From 8 to 14 years old
    - From 15 to 24 years old
    - From 25 to 35 years old

Other baseline variables:

- **Gender:** it is a nominal dichotomy qualitative variable, which will be divided in the following categories:
    - Male
    - Female

- **Intensive insulin treatment:** it is a nominal dichotomy qualitative variable. It will be divided in the following categories:
    - MDI: defined as a dose of long acting insulin offering a 24-hour control, plus a bolus of rapid acting insulin before each meal
    - CSII: the insulin is administrated in a continuous way during 24h with a pump trough a subcutaneous catheter

- **Time of diabetes evolution:** it will be considered as a quantitative discrete variable. It will be expressed as years from the onset to present.
- **Glycated hemoglobin at baseline:** it is a continuous quantitative variable expressed by a percentage. It will be evaluated by the following stratification:
    - 7.0% - 7.9%
    - 8.0 – 8.9%
    - > 9.0%

Measurement instruments

In order to obtain all the information related to the variables, we will use different measurement instruments.

Enrolment period:

- **Questionnaire:** Participants will be interviewed and screened according to the inclusion and exclusion criteria of the protocol with a questionnaire, which will be carried out by our researchers. It will include epidemiological information as gender, age, possibility of pregnancy, education, and clinical information related to diabetes. In this section, patients will be asked about the type of diabetes, time of evolution of the disease, persistence of the "Honeymoon", glycated hemoglobin at baseline, treatment received, ambulatory glucose control method used, the use of CGM system during the evolution of the disease and chronic complications affection **(Annex 2)**.

After the run-in period, we will collect all the variables information needed for the study with the following instruments:

- **Blood analysis**: it will be performed to measure the glycated hemoglobin at baseline and every 3 months during the intervention period. A venous blood sample will be obtained from the puncture of the cephalic or the basilica vein of the arm. Afterwards, it will be analyzed using the high efficacy liquid chromatography technique. The result will be expressed as a percentage.

- **"Modified Spanish Version of Diabetes Quality of Life Questionnaire".** It is a validated questionnaire adapted to the Spanish population, which was developed for patients with insulin-dependent Diabetes Mellitus. Four subscales measures life satisfaction, diabetes impact, worries about diabetes, and social and vocational concerns **(Annex 3)**.

- **Personal diary:** The participant will collect the information on acute complications during the intervention period in an ambulatory way. Each participant will document all the acute complications in a personal diary **(Annex 4)**. Referring to hypoglycemia, patients must register the capillary glycemic value, the symptoms percived and also the measure to correct it. In case of severe hypoglycemia, a medical report will be needed in case the participant needs medical assistance. For hyperglycemia, the documentation process will be the same as for hypoglycemia. Diabetic ketoacidosis episodes must be demonstrated by a blood analysis, and a medical report will be needed.

Information collection

Once the protocol of the study is completed, it will be submitted to the "*Comité Ètic d'Investigació Clínica*" of the "*Universitat Internacional de Catalunya*". During the enrolment period,

we will present the Informed Consent to take part in the study, as well as the information document for the participants, written according to the ethic principles of medical practice and the current laws.

All the endocrinologists from the selected hospitals who agree to collaborate with our research will form the medical team, who will be responsible for collecting all the data. All the specialists will also be trained on the way to collect the data, on the use of all the measurement instruments, and the different procedures to input the information into the data registry of the study.

Proceedings:

All the patients who comply with the inclusion criteria from the provided list will be invited to take part in the study. Taking into account the positive response to participate in the clinical trial, they will go through a selection process during which the participants will be interviewed and screened according to the inclusion and exclusion criteria of the protocol.

Considering that all the participants will need to know how to manage the ambulatory control system, all the participants who comply with the inclusion and exclusion criteria will take part in the training program. The legal tutors of all those participants who are less than 15 years old must take part in the training program. During this process, all the participants will receive training in general diabetes concepts, optimal levels of glycemic control, technical usage of CGM system, technical usage of SMBG system, insulin modification dose according to control results, etc.

When the enrolment period is over, we will start with the intervention period, which will take 13 months. Participants will be submitted to a control after being selected (month 0 from the intervention period) and before the randomization process. In the first visit we will perform the following procedures:

- A blood sample will be taken in order to analyze the glycated hemoglobin at baseline.
- Participants must answer the “Modified Spanish Version of Diabetes Quality of Life Questionnaire”. The obtained score will represent the baseline quality of life.

Participants from both groups will be followed during 13 months, and all of them will have to attend to the control every 3 months (16, 19, 22 and 25 from the study). In this visits the following procedures will be done:

- A blood sample will be taken in order to analyze the glycated hemoglobin.
- Participants must answer the "Modified Spanish Version of Diabetes Quality of Life Questionnaire".
- All acute complications will be collected in the register document.

All the data will be collected on paper. Afterwards all the registered information will be revised and integrated in an electronic database.

Statistical Analysis

Firstly, we will carry on the statistical analysis with a descriptive analysis of all the variables. Results from quantitative variables will be expressed as averages and standard deviations; frequencies and percentages will be used for qualitative variables.

Secondly, we will go trough the inferential statistics to contrast our hypothesis:

Objective 1: for the glycated hemoglobin variable, defined as a quantitative continuous variable, we will do two analyses. At first, to know if glycated hemoglobin is influenced by the ambulatory glucose control system used, we will use the T-Student test for independent variables. The second analysis will consist in finding if there are any variations in the glycated hemoglobin from the beginning of the study till the end of the study among the participants from the same group with the ANOVA test for repeated measures. In case our sample did not present a normal distribution of the participants, we would perform the statistical analysis with the non-parametrical tests U of Mann-Whitney and Kruskal-Wallis respectively.

Objective 2: To evaluate if there is a reduction of the acute complications with the CGM system compared to the SMBG system, we will use the T-Student test for independent variables, considering the system a dichotomy qualitative variable, and the number of complications a quantitative discrete variable. We will perform the analysis for each acute complication. In case our sample did not present a normal distribution of the participants, we would perform the statistical analysis with the non-parametrical tests U of Mann-Whitney.

Objective 3: to analyze if the glycated hemoglobin is influenced by the participants' age, we will stratify the sample according to the age in 3 categories in both intervention groups: from 8 to 14 years old, from 15 to 24 years old, and from 25 to 35 years old. To analyze two independent variables the first one, a continuous quantitative variable, and the second one an ordinal qualitative

variable, we will use the ANOVA test. In case our sample did not present a normal distribution of the participants, we would perform the statistical analysis with the non-parametrical Kruskal-Wallis test.

Objective 4: we will stratify the sample according to the studies level in 3 categories in both groups: primary school, high school, and graduate studies. To analyze two independent variables, the first one a quantitative variable, and the other one a non-dichotomy qualitative variable, we will use the ANOVA test. In case our sample did not present a normal distribution of the participants, we would perform the statistical analysis with the non-parametrical Kruskal-Wallis test.

Objective 5: for the quality of life variable, defined as a quantitative discrete variable, we will do two analyses. First, to know if the quality of life is influenced by the ambulatory glucose control system used, we will apply the T-Student test for independent variables. We will also analyze if there are any variations between the baseline and the end of the study among the participants from the same group with the ANOVA test for repeated measures. In case our sample did not present a normal distribution of the participants, we would perform the statistical analysis with the non-parametrical tests U of Mann-Whitney and Kruskal-Wallis respectively.

Finally we will also calculate an associating measure. The relative risk will be calculated in order to know if the intervention system results in a protective measure or not. The number of subjects needed to treat will be also analyzed in order to know how many patients we need to treat to get the glycated hemoglobin controlled well.

All the data obtained during the research and registered in the electronic database will be analyzed with the statistics program IBM SPSS Statistics Version 21 ®. We will use a confidence interval of 95% (CI 95%) and a *p-value* of less than 0.05 to indicate statistical significance.

Activity Chart

Our study will have 28 months of duration. We propose to start on July 2015 and we expect to finish the research at the end of 2017. The time distribution of each activity that we will carry out is showed on a chart divided by months in the **Annex 5**.

1) **Final revision of the Protocol:** this period will take 6 months (from month 1 to month 6 of the study). The first period will be integrated by all the activities related to the elaboration, and validation of the protocol:

- Protocol elaboration: we will complete the research protocol during the first 4 months. A meeting with all the researchers will also take place to improve the protocol.
- Protocol presentation to the "*Comité Ètic d'Investigació Clínica*" of the "*Universitat Internacional de Catalunya*", on the 5th month of the study.
- Database elaboration: we will perform an electronic database in order to register all the data during the study on the 6th month, before starting with the enrolment period.

2) **Enrolment period:** this period will take 6 months. During this period, we will cover all the activities related to the creation of the professional team, the patients' selection, and the sample we will focus on.
   - Researcher selection: the researcher team will be created during the 7th month of the study.
   - Presentation of the protocol to the reference hospitals and selection of the professional collaborators: once the protocol is finished and accepted by the ethical committee, we will present it to the hospitals of Vallès Occidental. During the 8th month of the study, all the professionals from the endocrinology units of the reference hospitals will be invited to join our professional team.
   - Training the collaborators on data collection process will be carried out during the 9th month.
   - Patients' medical history and invitation: during the 10th month of the study, we will collect all the medical histories from patients and will only select those who meet the inclusion criteria of the study.
   - Application of inclusion and exclusion criteria, patient training program and quiz: these activities will be carried out during the months 11 and 12 of the study.
   - Informed Consent: during the sample selection, all the patients will have to sign the Informed Consent to participate in the study.

3) **Intervention period:** this will take 13 months.
   - Baseline evaluation: it will be carried out during the month 13 of the study prior to randomization.
   - Randomization: we will randomly assign the participants to one of the study groups on the 13th month of the study.
   - Follow up: during 12 months (month 13 to month 25), participants will be followed up, and will attend to a control session every 3 months (month 16, 19, 22 and 25).

4) **Evaluation:** this period will take 3 months. It will include:

- Registration of the data in the electronic database.
- Statistical analysis.
- Final report elaboration.
- Results presentation and dissemination.

4. Ethical aspects and other considerations

The study will be carried out following all the ethic consideration about human medical experimentation included in the Declaration of Helsinki, and its successive revisions, and the Good Clinical Practice Rules. An Informed Consent **(Annex 6),** as well as an informative document **(Annex 7)** for the participants will be written according the ethic principles of medical practice and the current laws. After that, the protocol and the other documents will be evaluated by the "*Comité Ètic d'Investigació Clínica*" of the "*Universitat Internacional de Catalunya"*.

Regarding to the confidentiality data, just the researchers and professional collaborators (doctors and nurses) will have access to the participants' information. All the collaborators of the study will sign an ethical and confidentiality agreement in which they promise to use ethic and good clinical practice rules, and to protect the participants' data according to the*"Ley 41/2002, 14 de noviembre, básica reguladora de la autonomía del paciente y de derechos y obligaciones en material de información y documentación clínica".* All the personal data, analytic results and medical history of the participants, will be processed guaranteeing the protection and confidentiality of that by the anonymity according to the *"Ley Orgánica 15/1999, 13 de diciembre, de protección de datos de caracter personal"*.

All the participants will be informed orally and written about their voluntary participation, the research procedures, the risks and benefits, the possibility to step out if they desire it, confidentiality, and the anonymous character of all their data. It will be necessary, that all the participants or their legal tutors, in case they are younger than 18 years old, sign the Informed Consent before starting the intervention period.

5. Limitations and strengths

There are some methodological limitations in our study that have to be taken into account. In this research no blinding techniques will be used because both evaluated systems are invasive techniques, which will be controlled by the participants in an ambulatory way. Thus, they must know the technique used in order to obtain a good self-management.

The voluntary participation may induce a selection bias. Patients who are controlled well, and interested in new technologies to handle their disease may draw to select a non-representative sample.

As we will work with 4 hospitals, it is possible that they might not be as homogeneous as desired, so the professional team or the patients from each center will have some differences among them. However, we will try to minimize this limitation by the training program for the professionals.

Finally, the last limitation is related to data collection. All the acute complications should be collected and registered in a personal diary. In addition, the quality of this self-reported data relies on the patient, however clear instructions will be given to diminish this potential information bias. Unfortunately, not all of them are perceived by the patient. On the one hand, patients from CGM system group will have the opportunity to register all the data thanks to the memory of the sensor. On the other hand, patients from SMBG system group, as its technique does not count with a memory device, will not be able to register the unnoticed complications. This might wrongly seem that the CGM system provokes more complications than the SMBG system. Because of that, we will just count for the analysis as acute complication the ones, which have been perceived with symptoms by the participant.

There will also be some strengths in this research, which may be taken into account. Firstly, it is important to focus on the study design, which will be a randomized controlled trial. This is the best design to obtain high quality scientific evidence. It is important to mention that there have not been carried out similar studies in Spain, so it will be the first study that compares the CGM system and the SMBG system in our country. In addition, it is a feasible study that has not been carried out before in our country, economically viable with a significant sample.

6. Expected Outcome

According to our hypothesis, we expect to obtain a higher reduction (0,5-1%) of the glycated hemoglobin in the CGM system group.

We also think that differences between diabetes control will be observed between age ranges, so patients older than 25 will achieve better glycemic patterns. Another relevant result will be the differences obtained in the glycemic control independently of the system used, in which the highest studies level the better control achieved. Finally, a better quality of life will be reported on the CGM system group, because of the possibility to obtain the blood glucose level without a puncture, and the glucose curve of the whole day.

The main indicator of those results will be the decrease of glycated hemoglobin and the decrease of acute complications. The indicator that will objectify the improvement of quality of life with the CGM system will be the score obtained according to the "Modified Spanish Version of Diabetes Quality of Life Questionnaire".

The main beneficiaries of the CGM system will be Type 1 diabetes patients, older than 25 years old, with studies.

Results are going to be published in scientific journals, as well as endocrinologist and diabetes specialized journals. We would also diseminate the results in national and international medical meetings in order to let professionals know about our research. It would also be important to elaborate new guidelines including the CGM system as an alternative to the SMBG system for the ambulatory glucose control.

Finally it would be very important to propose future scientific researches to study the applicability of the CGM system to diabetic population with other characteristics (older and younger patients, pregnant patients, bad controlled patients etc.).

7. Collaborating Team

Name: Berta Ferran Ballús

Qualification: Graduate in Medicine and Surgery. Main Investigator.

Role in the project: The main investigator will be the person responsible of the protocol elaboration, presentation to the ethical committee, execution of the study, coordination of the four participant hospitals and coordination of the research team. The main investigator will also carry out the results redaction and the study publication.

Qualification: Specialists in Endocrinology.

Role in the project: A minimum of two endocrinologists of each hospital will collaborate with the research by providing the medical histories' of patients that complain with the diagnostic, the age and the time of evolution. They will be the responsible of collecting all the data during the follow-up.

Qualification: Nurses.

Role in the project: A minimum of two nurses specialized in endocrinology of each hospital will collaborate with the research by performing the blood analysis during the follow-up. They will also perform the "Modified Spanish Version of Diabetes Quality of Life Questionnaire" at baseline and in each control session.

Qualification: Laboratory technic.

Role in the project: one laboratory technic from each hospital will analyze the blood samples of all the patients. They will provide the glycated hemoglobin results as well as other parameters.

Qualification: Statistician.

Role in the project: The statistician will be the person responsible of elaborate the statistical plan, the estimation of the sample size and the analysis of the obtained results.

Qualification: Computer technician.

Role in the project: perform an electronic database in order to regiser all the data during the study according to the *"Ley Orgánica 15/1999, 13 de diciembre, de protección de datos de caracter personal"*, and finally enter all the data obtained during the study on it.

Qualification: Project manager.

Role in the project: estimate the budget of the study.

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Annex

Annex 1: Interpretation of the Glycated Hemoglobin levels.

HbA1c	6% - 6,9%	7% - 7,9%	8 – 8,9%	9 – 9,9%	> 10%
Glycemic average (mg/dl)	130 - 155	155 - 180	180 - 210	210 - 270	270 - 300
					
Complications risk	Very low	Moderate	High	Very high	Critic
Target HbA1c: < 7%					

Annex 2: Enrolment survey

Nom:

Data de Naixement:

Dades Epidemiològiques:

1. Sexe
   a. Masculí ☐
   b. Femení ☐
      - Possibilitat d'embaràs?
        Sí ☐
        No ☐

2. Nivell d'estudis
   a. Primària ☐
   b. Secundària ☐
   c. Superiors ☐

3. Edat ☐ anys

Dades relacionades amb la Diabetis:

4. Tipus de Diabetis
    a. Diabetis Mellitus Tipus 1 ☐
    b. Diabetis Mellitus Tipus 2 ☐
    c. Altres ☐

5. Temps d'evolució de la Diabetis
    ☐ Anys
        - En cas de curta evolució (menys de 2 anys) persisteix en fase de "Lluna de Mel?"

            Sí ☐ No ☐

6. Hemoglobina glucosilada en l'última analítica: ☐ %

7. Tractament
    a. Multiples Injeccions Diàries ☐
    b. Infusió contínua d'insulina subcutània ☐
    c. Altres ☐

8. Mètode de control ambulatori de glucosa
    a. Monitorització Contínua de la Glucosa ☐
    b. Automonitorització de la glucos en sang ☐
    c. Altres ☐

9. Prèvia utilització del sistema CGM
    a. Sí ☐
    b. No ☐

10. El pacient presenta complicacions cròniques?
    a. Sí ☐
    b. No ☐

Annex 3: M.M.Millán JR, J.Del Campo. Revaloración de la versión española del questionario Diabetes Quality of Life (EsDQoL). Endocrinología y Nutrición 2002;49(10):322-4.

Satisfacción

1. ¿Está usted satisfecho con la cantidad de tiempo que tarda en controlar su diabetes?
2. ¿Está usted satisfecho con la cantidad de tiempo que ocupa en revisiones?
3. ¿Está usted satisfecho con el tiempo que tarda en determinar su nivel de azúcar?
4. ¿Está usted satisfecho con su tratamiento actual?
5. ¿Está usted satisfecho con la flexibilidad que tiene en su dieta?
6. ¿Está usted satisfecho con la carga que supone su diabetes en su familia?
7. ¿Está usted satisfecho con su conocimiento sobre la diabetes?
8. ¿Está usted satisfecho con su sueño?
9. ¿Está usted satisfecho con sus relaciones sociales y amistades?
10. ¿Está usted satisfecho con su vida sexual?
11. ¿Está usted satisfecho con sus actividades en el trabajo, colegio u hogar?
12. ¿Está usted satisfecho con la apariencia de su cuerpo?
13. ¿Está usted satisfecho con el tiempo que emplea haciendo ejercicio?
14. ¿Está usted satisfecho con su tiempo libre?
15. ¿Está usted satisfecho con su vida en general?

Impacto

16. ¿Con qué frecuencia siente dolor asociado con el tratamiento de su diabetes?
17. ¿Con qué frecuencia se siente avergonzado por tener que tratar su diabetes en público?
18. ¿Con qué frecuencia se siente físicamente enfermo?
19. ¿Con qué frecuencia su diabetes interfiere en su vida familiar?
20. ¿Con qué frecuencia tiene problemas para dormir?
21. ¿Con qué frecuencia encuentra que su diabetes limita sus relaciones sociales y amistades?
22. ¿Con qué frecuencia se siente restringido por su dieta?
23. ¿Con qué frecuencia su diabetes interfiere en su vida sexual?
24. ¿Con qué frecuencia su diabetes le impide conducir o usar una máquina (p. ej. máquina de escribir)?
25. ¿Con qué frecuencia su diabetes interfiere en la realización de ejercicio?
26. ¿Con qué frecuencia abandona sus tareas en el trabajo, colegio o casa por su diabetes?
27. ¿Con qué frecuencia se encuentra usted mismo explicándose qué significa tener diabetes?
28. ¿Con qué frecuencia cree que su diabetes interrumpe sus actividades de tiempo libre?
29. ¿Con qué frecuencia bromean con usted por causa de su diabetes?
30. ¿Con qué frecuencia siente que por su diabetes va al cuarto de baño más que los demás?
31. ¿Con qué frecuencia come algo que no debe antes de decirle a alguien que tiene diabetes?
32. ¿Con qué frecuencia esconde a los demás el hecho de que usted está teniendo una reacción insulínica?

Preocupación: social/vocacional

33. ¿Con qué frecuencia le preocupa si se casará?
34. ¿Con qué frecuencia le preocupa si tendrá hijos?
35. ¿Con qué frecuencia le preocupa si conseguirá el trabajo que desea?
36. ¿Con qué frecuencia le preocupa si le será denegado un seguro?
37. ¿Con qué frecuencia le preocupa si será capaz de completar su educación?
38. ¿Con qué frecuencia le preocupa si perderá el empleo?
39. ¿Con qué frecuencia le preocupa si podrá ir de vacaciones o de viaje?

Preocupación: relacionada con la diabetes

40. ¿Con qué frecuencia le preocupa si perderá el conocimiento?
41. ¿Con qué frecuencia le preocupa que su cuerpo parezca diferente a causa de su diabetes?
42. ¿Con qué frecuencia le preocupa si tendrá complicaciones debidas a su diabetes?
43. ¿Con qué frecuencia le preocupa si alguien no saldrá con usted a causa de su diabetes?

Endocrinol Nutr. 2002;49:322

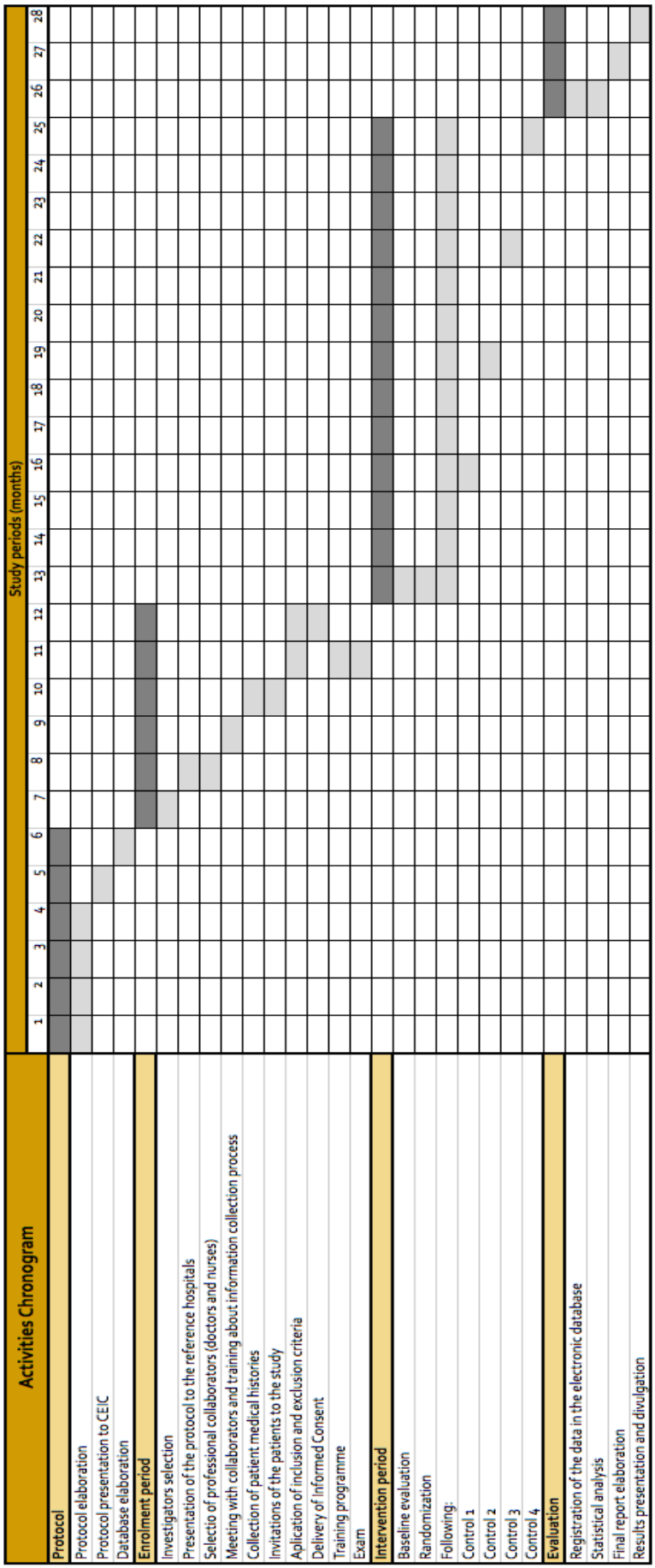
Annex 4: Personal diary

1. Hipoglucèmia
    a. Glucèmia ☐ mg/dl
    b. Percepció dels símptomes d'hipoglucèmia?
        - Sí ☐
        - No ☐
    c. Mesura correctora:
    d. Necessitat d'assistència sanitària:
        - Sí ☐ → Adjuntar informe mèdic
        - No ☐

2. Hiperglucèmia
    a. Glucèmia ☐ mg/dl
    b. Percepció dels símptomes d'hiperglucèmia?
        - Sí ☐
        - No ☐
    c. Mesura correctora:
    d. Necessitat d'assistència sanitària:
        - Sí ☐ → Adjuntar informe mèdic
        - No ☐

3. Cetoacidosi Diabètica
    a. Adjuntar informe mèdic + Analítica

Annex 5: Activity Chart



Annex 6: Information document for the patient.

DOCUMENT D'INFORMACIÓ AL PACIENT

Títol de l'estudi: Control glucèmic de la Diabetis Mellitus tipus 1 amb el sistema de Monitorització Contínua de la Glucosa comparat amb el sistema d'Automonotorització de la glucosa en sang: un assaig clínic aleatoritzat.

Investigador Principal: Berta Ferran Ballús, Graduada en Medicina i Cirurgia.
Centre: Universitat Internacional de Catalunya

Benvolgut Sr./Sra.,

Ens dirigim a vostè per informar-lo sobre un estudi d'investigació en el que el convidem a participar. L'estudi ha estat aprovat pel Comitè Ètic d'Investigació Clínica de la Universitat Internacional de Catalunya, d'acord amb la vigent legislació, i es durà a terme amb total respecte pels principis ètics acceptats en investigació biomèdica amb éssers humans i les normes de la Bona Pràctica Clínica.

La intenció d'aquest document es que vostè rebi la informació correcta i suficient per tal que vostè pugui avaluar i jutjar si decideix o no participar en aquest estudi. Per això, cal que llegeixi detingudament aquest document informatiu i podrà contactar amb el representant de l'estudi del seu centre hospitalari per tal d'obtenir respostes a preguntes pertinents sobre la investigació, incloent-hi inquietuts i queixes. A més, pot consultar al Comitè Ètic d'Investigació Clínica de la Universitat Internacional de Catalunya per a dubtes relacionats amb els drets dels participants en la investigació clínica.

Ha de saber que la participació en aquest estudi és totalment voluntària i que pot decidir no participar o canviar la seva decisió i retirar el consentiment en qualsevol moment, sense qua per això s'alteri la relació amb el seu metge ni que es produeixi cap prejudici en el seu control i tractament.

DESCRIPCIÓ GENERAL DE L'ESTUDI

Aquest projecte s'ha creat amb la intenció d'estudiar i determinar quin dels sistemes de control ambulatori de la glucosa permet aconseguir un millor control glucèmic. El control glicèmic

estandarditzat dels pacients amb Diabetis Tipus 1 en el nostre medi, consisteix en la Automonitorització de la glucosa en sang mitjançant un glucòmetre convencional després de cada àpat i abans d'anar a dormir a més dels controls que el pacient cregui necessàries en situacions d'hiperglucèmia o hipoglucèmia. A més, també s'analitza de manera trimestral o semestral la hemoglobina glicosilada mitjançant una analítica sanguínia convencional, paràmetre que permet tenir el coneixement de la mitjana de la glucèmia durant els darrers tres mesos.

Tot i el control estricte de la glucèmia capil·lar junt amb la hemoglobina glicosilada i el tractament intensiu amb insulina, sovint els pacients amb Diabetis Mellitus Tipus 1, no aconsegueixen un control òptim dels nivells glucèmics. Darrerament, s'ha començat a comercialitzar a Espanya el primer sistema de Monitorització Contínua de la Glucosa. Aquest dispositiu, és un nou sistema per al control ambulatori de la glucosa que permet conèixer el nivell de glucosa en sang sense necessitat de punxar-se, sense utilitzar tires reactives i sense sang. Aquest consisteix en un sensor instal·lat al teixit subcutani del braç, que recull i emmagatzema els nivells de glucosa durant el dia i la nit de manera contínua. Mitjançant l'escàner del sensor mitjançant un lector, s'obté el valor actual de glucosa, la corba dels valors de les últimes hores i una fletxa que indica la tendència de la glucosa en aquell moment.

El fet de tractar-se d'un sistema de tant recent comercialització, i la falta d'experiència amb aquest en el nostra medi, fa que a dia d'avui encara no es coneguin amb exactitud les seves aplicacions, ni els potencials beneficis que podria aportar a la població amb Diabetis Tipus 1. Per això, l'objectiu principal d'aquest estudi, es avaluar si el sistema de Monotorització Contínua de la Glucosa permet una disminució de la hemoglobina glicosilada major que el sistema convencional d'Automonotorització de la glucosa en sang. També formen part dels nostre objectius determinar com l'edat del pacient o el nivell d'estudis podrien influenciar en el control de la Diabetis Mellitus tipus 1. Finalment, s'avaluarà quin dels dos sistemes a estudiar proporciona un major nivell de qualitat de vida als pacients.

El mètode utilitzat per dur a terme aquest estudi consistirà en la selecció de 190 pacients dels quatre hospitals de referència del Vallès Occidental amb Diabetis Tipus 1, amb una edat compresa entre 8 i 35 anys i una evolució de la malaltia major de 18 mesos. Abans d'iniciar l'estudi, els pacients seleccionats participaran en una sessió de formació on s'explicarà el sistema de funcionament de cada sistema de control. Posteriorment seran sotmesos a una primera avaluació on es durà a terme un anàlisi de sang per determinar el nivell de hemoglobina glicosilada a l'inici de l'estudi, un qüestionari per avaluar el nivell de qualitat de vida, un qüestionari per recollir dades epidemiològiques dels participants. Un cop realitzada la primera avaluació, els participants seran dividits en dos grups que rebran un o l'altre sistema de control ambulatori de la glucosa. Els

participants seran seguits durant 12 mesos i es citaran a consulta cada 3 mesos on se'ls realitzarà seriadament una analítica. En l'última visita a més s'administrarà de nou el qüestionari que avalua el nivell de qualitat de vida.

BENEFICIS I RISCOS DERIVATS DE LA SEVA PARTICIPACIÓ A L'ESTUDI:

Els beneficis esperats per a vostè comprenen la millora del seu perfil glucèmic, la disminució de les complicacions agudes pròpies de la seva malaltia (hiperglucèmia, hipoglucèmia i cetoacidosi diabètica) i una millora en el seu nivell de qualitat de vida. A més també, rebrà una sessió de formació que li permetrà una actualització dels coneixements en relació a la seva malaltia.

L'experiència amb els dos sistemes de control, malgrat només n'hi hagi un d'estandaritzat en el nostra medi ha estat positiva. Per això no s'espera que hagi d'haver cap efecte advers derivat de cap dels sistemes de control. En cas que un dels dos sistemes mostri superioritat en el control de la Diabetis respecte l'altre, en cas d'utilitzar el sistema que no experimenti milloria del control glucèmic, no implica que el seu control hagi empitjorat.

CONFIDENCIALITAT

El tractament, la comunicació i la cessió de dades de caràcter personal de tots els subjectes participants s'ajustarà a l'exposat en la Llei Orgànica 15/1999, del 13 de desembre, de protecció de dades de caràcter personal. D'acord al que estableix la legislació mencionada, vostè pot exercir el dret d'accés, modificació, oposició i cancel·lació de dades, pel qual s'haurà de dirigir al seu metge de l'estudi. La seva identitat no serà revelada a cap personal a excepte en cas d'urgència mèdica o requeriment legal.

Només es transmetran a tercers les dades recollides a l'estudi pels mateixos fins que els descrits en aquesta investigació, i serà sempre preservant la confidencialitat amb el nivell de la legislació vigent en el nostre país.

L'accés a la seva informació personal quedarà restringida al metge de l'estudi, investigadors i col·laboradadors, al Comitè Ètic d'Investigació Clínica i personal autoritzat, quan es precisi, per comprovar les dades i procediments de l'estudi, sempre mantenint la confidencialitat dels mateixos d'acord a la legislació vigent.

COMPENSACIÓ ECONÒMICA:

El promotor de l'estudi es el responsable de gestionar el finançament del mateix. La seva participació a l'estudi no li suposarà cap despesa i se'ls reembolsarà, en cas que n'hi hagués, qualsevol despesa extraordinària. Vostè no haurà de pagar els sistemes de control ambulatori de la glucosa, ni els procediments a que es sotmetrà durant el seguiment.

ALTRA INFORMACIÓ RELLEVANT:

Qualsevol nova informació referent al sistema de control utilitzat en l'estudi que pugui afectar la seva disposició a participar a l'estudi, que es descobreixi durant la seva participació, li serà comunicada pel seu metge de seguida.

Si vostè decideix retirar el consentiment per participar a l'estudi, cap dada nova s'introduirà a la base de dades, i podrà exigir la destrucció de totes les mostres identificables prèviament retingudaes per a la realització de futurs anàlisis.

També ha de saber que pot ser exclòs de l'estudi si el promotor o els investigadors de l'estudi ho consideren oportú, ja sigui per motius de seguretat, per qualsevol esdeveniment advers que es produís pel sistema de control, o perquè es consideri que no compleix amb els procediments establerts. En qualsevol dels casos, vostè rebrà una explicació adequada del motiu que hagi ocasionat la seva retirada de l'estudi.

En firma el consentiment adjunt, vostè es compromet a complir amb els procediments de l'estudi exposats.

Cordialment,

Berta Ferran Ballús
Investigadora principal de l'estudi

Annex 7: Informed Consent.

CONSENTIMENT INFORMAT PER A PARTICIPAR A L'ESTUDI

Títol de l'estudi: Control glucèmic de la Diabetis Mellitus tipus 1 amb el sistema de Monitorització Contínua de la Glucosa comparat amb el sistema d'Automonotorització de la glucosa en sang: un assaig clínic aleatoritzat.

Benvolgut Sr./Sra.,

Firmant aquest consentiment, vostè accedeix a participar a l'estudi i dóna permís per a l'ús i publicació de les dades que ens faciliti en els procediments de la investigació respectant sempre l'anonimat. Si vostè no està d'acord, no hauria de signar aquest document, i així denega la seva participació a l'estudi.

Sr./Sra. ..... amb DNI ....., en ple ús de les meves facultats mentals i en qualitat de pacient:

DECLARO: que he llegit el document amb les explicacions que detallen els objectius i característiques d'aquest estudi, les he comprès i estic conforme amb elles. Se m'ha infromat satisfactòriament en relació als detalls que implica la participació a l'estudi, els he comprès i estic d'acord amb ells. S'han resolt totes les meves preguntes i de manera entenedora i he comprès correctament tot el procés de l'estudi. Per això, dono el meu consentiment voluntari a participar en aquesta investigació i d'acord a les lleis espanyoles i autonòmiques que em protegeixen.

A ....., a ..... de ..... de 20 ..... .

Signatura del pacient:

Nom i cognoms de l'investigador ..... .

Signatura de l'investigador:
