Randomized multicentric clinical trial to assess the efficacy of the system Insulclock® for insulin treatment management in type 1 diabetes patients with insufficient glycemic control.

Date:	January 9th, 2021
Principal investigator:	Dr. Fernando Gómez Peralta

1. ABSTRACT

1.1. PRINCIPAL INVESTIGATOR

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1.2. TRIAL TITLE

Randomized multicentric clinical trial to assess the efficacy of the system Insulclock® for insulin treatment management with type 1 diabetes patients with insufficient glycemic control.

1.3. TYPE OF CENTERS WHERE THE TRIAL WILL BE CARRIED OUT

The trial will be carried out in:

- Endocrinology and Nutrition Unit /Diabetes Unit, Hospital General de Segovia. Segovia, Spain
- Endocrinology and Nutrition Service, Hospital de Cruces. Bilbao, Spain
- Endocrinology and Nutrition Unit, Arquitecto Marcide Hospital, Ferrol, A Coruña, Spain
- Endocrinology and Nutrition Service, Hospital Central de Asturias, Oviedo, Spain

1.4. CREC ASSESSING THE TRIAL

The trial protocol has been classified by the Spanish Medicines and Healthcare Products Agency (AEMPS) and approved by the reference CREC.

1.5. MAIN AIM OF THE TRIAL

Determine if the Insulclock® insulin therapy management system can improve time in range compared to the standard follow-up in uncontrolled type 1 diabetes patients.

1.6. DESIGN

Randomized open-label multicenter controlled trial.

1.7. ILLNESS IN THE TRIAL

Type 1 Diabetes Mellitus (DM1)

1.8. TRIAL POPULATION AND NUMBER OF PARTICIPANTS

80 type 1 diabetes subjects with insufficient glycemic control.

1.9. ESTIMATED TIME SCHEDULE

Period of inclusion beginning.	March 2021
Period of inclusion end.	July 2021
Following period end.	September 2021
Data analysis	October-December 2021
Send to congresses and publication.	December 2021

TABLE OF CONTENTS

1. ABSTRACT 3

1.1. PRINCIPAL INVESTIGATOR 3

1.2. TRIAL TITLE 3

1.3. TYPE OF CENTERS WHERE THE TRIAL WILL BE CARRIED OUT 3

1.4. CREC ASSESSING THE TRIAL 3

1.5. MAIN AIM OF THE TRIAL 3

1.6. DESIGN 3

1.7. ILLNESS IN THE TRIAL 3

1.8. TRIAL POPULATION AND NUMBER OF PARTICIPANTS 3

1.9. ESTIMATED TIME SCHEDULE 3

2. GENERAL INFORMATION 6

2.1. TRIAL IDENTIFICATION 6

2.1.1. TITLE 6

2.1.2. TYPE OF TRIAL 6

2.1.3. CREC ASSESSING THE TRIAL 6

2.1.4. EXPECTED DURATION 6

3. JUSTIFICATION OF THE TRIAL 6

4. DEVICES 8

4.1. INSULCLOCK SYSTEM 8

4.2. CONTINUOUS GLUCOSE MONITORING (CGM) 9

6. BIBLIOGRAPHY 10

7. OBJECTIVES 12

8. INFORMATION SOURCES AND SCOPE 12

9. TRIAL DESIGN 12

9.1. TYPE OF CLINICAL TRIAL 12

9.2. STUDY POPULATION CHARACTERISTICS 13

9.2.1 INCLUSION CRITERIA 13

9.2.2. EXCLUSION CRITERIA 13

9.3. DETERMINE THE SIZE OF THE POPULATION 13

10. VARIABLES AND MEASURING INSTRUMENTS 14

11. PROTOCOL DESCRIPTION 14
11.1. DESIGN 14
11.2. TRIAL DURATION 15
11.3. PATIENTS SELECTION. NUMBER OF EXPECTED SUBJECTS. 15
11.4. METHODS: STUDY VISITS 15
12. STATISTICAL ANALYSIS 17
12.1. INTRODUCTION AND GENERALITIES. 17
12.2. STATISTICAL ANALYSIS 17
13. ETHICAL ASPECTS 17
13.1. GENERAL CONSIDERATIONS 17
13.2. BENEFIT-RISK ASSESSMENT 17
13.3. INFORMATION SHEET AND CONSENT FORM 18
13.4. CONFIDENTIALITY OF DATA 18
13.5. INTERFERENCE WITH PHYSICIAN'S PRESCRIBING HABITS 18
14. PRACTICAL CONSIDERATIONS 18
14.1. WORK PLAN 18
14.2. FINAL AND FOLLOW-UP REPORTS 18
14.3. PUBLICATION CONDITIONS 18
14.4. RESPONSIBILITIES OF THE PRINCIPAL INVESTIGATOR 19
14.5. RESPONSIBILITIES OF THE SITE INVESTIGATORS 19
Annexed 1. Clinical Research Ethics Committee Approval 20
Annexed 2. Patient information sheet 21
Annexed 3. Informed Consent Form 23

2. GENERAL INFORMATION

2.1. TRIAL IDENTIFICATION

2.1.1. TITLE

Randomized clinical trial to assess the efficacy of the system Insulclock® for insulin treatment management with type 1 diabetes patients with insufficient glycemic control.

2.1.2. TYPE OF TRIAL

The trial will be carried out in:

- Endocrinology and Nutrition Unit /Diabetes Unit, Hospital General de Segovia. Segovia, Spain
- Endocrinology and Nutrition Service, Hospital de Cruces. Bilbao, Spain
- Endocrinology and Nutrition Unit, Hospital Arquitecto Marcide, Ferrol, A Coruña, Spain
- Endocrinology and Nutrition Service, Hospital Central de Asturias, Oviedo, Spain

2.1.3. CREC ASSESSING THE TRIAL

The trial has been assessed and approved by the reference CREC.

2.1.4. EXPECTED DURATION

The expected duration of the trial will be six months.

Period of inclusion beginning.	March 2021
Period of inclusion end.	July 2021
Following period end.	September 2021
Data analysis	October-December 2021

3. JUSTIFICATION OF THE TRIAL

Diabetes mellitus (DM) is defined as hyperglycemia due to insufficient insulin secretion, inadequate insulin action, or both causes. Treatment of diabetes implies the need for lifestyle changes: diet, exercise, administration of hypoglycemic drugs and insulin, and blood glucose monitoring. In addition, diabetics may be at greater risk or predisposition to develop macrovascular complications (ischemic heart disease, stroke, lower-extremity ischemia) and microvascular (retinopathy, nephropathy, and neuropathy)[1,2,3]

DM groups two main clinical entities: type 1 diabetes (DM1) and type 2 (DM2), which are differentiated by their epidemiological and clinical characteristics, genetic and immunological, as reflected in multiple reports, among which the 1985[4] WHO report and the Consensus document for the care of people with diabetes in Spain should be highlighted[5].

In our country, the total prevalence of DM adjusted for age and sex was 13.8%. Of these, almost half did not know they had the disease (6.0%).[6] The annual incidence rate of DM1 in Spain, for the group under 15 years of age, is approximately 10-17 / 100,000.[7] The incidence rate of DM1 changes among Spanish regions. In the last 20 years, several epidemiological studies on DM1 have been developed in almost the entire Spanish geography. Most of the registries were carried out in a population under 15 years of age, while others included patients

under 30 years of age. Although, the methodology initially used was heterogeneous, standard lines of work have been defined to facilitate comparison of the results obtained.[8]

To avoid chronic complications, it is essential to maintain good glycemic control. Glycemic control is understood to be all the measures that facilitate maintaining blood glucose values close to normality limits. Strict glycemic control reduces microvascular complications in DM1.[9-10]

Many factors can influence intensive glycemic control, including demographic and psychosocial factors, such as age, motivation, compliance, diabetes education, and disease management skills.[11] Another key barrier to intensive insulin management is the fear of hypoglycemia. However, patients can reduce their risk through comprehensive self-care education and the use of new insulin therapy regimens.[12]

Low adherence to insulin regimens is common, reported occurring in up to two-thirds of patients with diabetes.[13] The most common barriers to injectable insulin therapy are socio-economic factors, the complexity of treatment, and adherence to the dosage prescribed, leading to frequent insulin omissions. These are registered in more than half of the patients with DM.[14] Therefore, it is crucial to identify patients at risk and develop strategies and tools to increase adherence to prescribed insulin regimens. Recent advancements in this field include the availability of electronic reminders, mobile communication technology such as telephone short message services,[15] smartphones or smartwatch wristbands,[16] and a variety of insulin pens with memory functions and electronic displays.[17-19]

Our previously published RSD1 study describes metabolic control and other indicators of adherence to treatment in people with DM1 in Castilla y León (Spain). It showed that the follow-up data and health outcomes are far from the optimal goal: the average HbA1c is 7.7%, only 21% of them below 7% and almost 50% have required hospitalization due to metabolic decompensation.[20] Insulin injection compliance is a major problem in people with DM1. Mechanisms to support patients, parents or partners to monitor injection compliance could improve insulin injection frequency. The omission of the insulin bolus before meals has been considered one reason for the worsening of glycemic control. An increase in hemoglobin A1c (HbA1c) of 1% has been estimated for every four pre-meal boluses missed per week in pediatric patients.[21] A decrease in HbA1c in the magnitude of 0.5% is clinically relevant for this population of patients, as shown in the Diabetes Control and Complications Trial.[22] Clinical experience indicates that a group of DM1 patients consistently have very poor control. Some of them even regularly attend their doctor and educator visits without improving it.[23]

Some studies have identified a group of DM1 patients with constant poor control, with HbA1c maintained at a moderately high (9.1% to 11.0%) or very high (greater than 11.0%) reference level. This group generally contained almost a third of the entire sample.[24] Alternatives appear to be necessary to improve their control.

Insulclock®[25] is a system based on a small electronic device easily attached to all insulin pen devices to collect critical information about the date, time and dose of each injection, type of insulin used, and temperature. Insulclock® has an alarm system, visual and audible, to avoid the omission of insulin and delays. Via Bluetooth and smartphone technology, the information is stored and available for analysis by patients, caregivers and healthcare professionals. Insulclock® real-time memory and alert system could improve glycemic control compared to conventional insulin pen devices due to improved injection control and adherence[26].

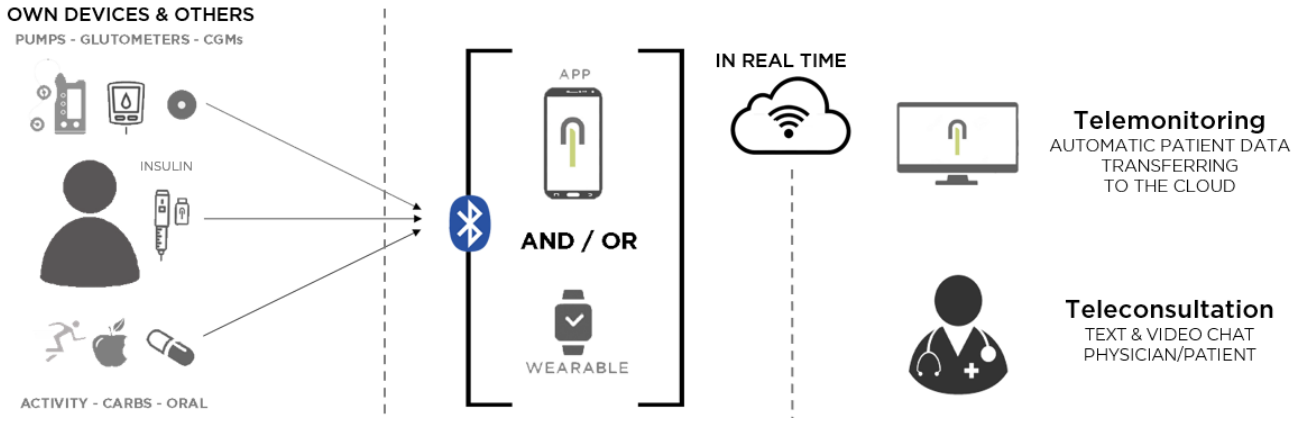
Before considering the current multicenter study, we have conducted a randomized controlled pilot study that has already assessed the clinical impact of Insulclock® on glycemic control and variability, adherence to treatment and satisfaction in persistently uncontrolled DM1 patients. Additionally, glycemic variability was measured with continuous glucose monitoring *FreeStyle Libre*™. Glucometrics included glucose variation coefficient (CV), standard deviation (SD), time in range (TIR), time above range (TAR), and time below range (TBR). To identify glucose excursions in meals, we use the Glucose Rate Increase Detector (GRID) algorithm, which estimates the rate of change (ROC) of glucose from CGM data.

Sixteen patients completed the study: 10 in the Active group and 6 in the Masked group. The use of Insulclock® was associated with a decrease in average glucose (-27.0 mg/dL; P -0.013), standard glucose deviation (-14.4mg/dL; P x 0.003), and the time above the range (-12.5%; P x 0.0026), and an increase in time in range (TIR) (+7%; P. 0.038) in the entire group. The use of application information and alerts in the active group was associated with an increase in TIR (+8%; P x 0.026). We observed a reduction of -3.9 (P x 0.1352) and -5.4 (P x 0.032) per month in the number of forgotten insulin doses and delayed in the entire group. Most Insulin Treatment Satisfaction Questionnaire (ITSQ) elements improved after four weeks of use of Insulclock®. This pilot study showed that Insulclock® contributes to improved glycemic control (including variability), decreasing missed and delayed insulin doses, and improves satisfaction with treatment in persistently poorly controlled DM1 patients.[27]

4. DEVICES

4.1. INSULCLOCK SYSTEM

INSULCLOCK SYSTEM, is a product to monitor and control the treatment of a patient with Diabetes Mellitus (DM) as well as ease patient self-management. It is a comprehensive diabetes management platform encompassing a mobile app (Insulclock 360) connected via Bluetooth with the Insulclock insulin pen cap device, manufactured by Insulcloud S.L., and other devices (glucometers, CGMs…) developed by third parties. The system transfers all data to the cloud and shows it on a web platform that provides for single screen tracking of all patients for the physician.



The mobile application, developed natively for iOS and Android, creates reminders so that the patient does not forget to inject insulin, thus seeking to improve adherence to treatment. It also creates reminders that alert the patients to perform blood glucose tests, thus improving the control of their disease. Both types of reminders seek to minimize the situations that may lead the patient to suffer hypoglycemia or hyperglycemia episodes. In turn, the system involves the caregiver of the patient or the endocrinologist or diabetes educator, keeping them informed about the evolution of the patient, by sending notifications via email.

By collecting patient data (glucose, insulin, food intakes, physical activity and oral medication) the software calculates recommendations taking into account characteristic values of each patient. Based on these data provided by the patient, the Insulclock 360 mobile application will be able to recommend to the patient how much insulin to inject (bolus). Based on the patient's data, the software models the effect of insulin, not only its total effect but also when this effect occurs. With this, the software further improves the bolus calculator (previous module), since it knows how much active insulin is left from the previous injection, something that must be taken into account to improve the precision of the calculation.

With this data, the software also includes a blood glucose level predictor. Thanks to this, even if the patient does not want to enter the data of what he/she eats, the software can predict probable hypoglycemia episodes with a margin of time before it occurs, giving the patient time to take measurements.

In addition, the product has other functionalities, such as:

- Save glucose levels manually, embedding data from Healthkit (Apple) or automatically reading data from capillary glucometers, continuous glucose monitors or flash glucose readers compatible with the system.
- Automatically compose and fill in the diabetic diary by monitoring insulin doses, blood glucose levels, the notes that the patient wishes to create related to their disease, the physical activity that the patient performs and the images of the foods you eat.
- Establish a direct communication channel between patients and their endocrinologist or diabetes educator, allowing access to properly presented patient data in real time, with various graphs and statistics calculated from patient's data. Both the mobile application and the web platform have a chat and video-chat system so that the patient and endocrinologist or diabetes educator can be in contact when health professionals so desire.

The Insulclock insulin pen cap device transforms the insulin pen into a smart insulin pen, leveraging the moment of insulin delivery to automate data entry, and interfacing drug injection with the digital world of smartphones, PCs, tablets, and the cloud, thus helping the patient to record the administration of the treatment (automatically know when, how much and what type of insulin the patient has injected)

The Insulclock insulin pen cap device is compatible with the following disposable insulin pens from Lilly, Novo Nordisk and Sanofi. **Insulclock for Kwikpen (Lilly)**: Kwikpen Humulin Nph, Kwikpen Humalog, Kwikpen Humalog Mix 75/25, Kwikpen Humalog 200, Kwikpen Humulin 30:70, Kwikpen Humalog Basal, Kwikpen Humalog Mix 50, Kwikpen Humalog Junior, Kwikpen Abasaglar; **Insulclock for Solostar (Sanofi)**: Solostar Lantus, Solostar Apidra, Solostar Toujeo; Insulclock for Flexpen (Novo Nordisk): Flexpen Novomix30, Flexpen Novomix50, Flexpen Novomix70, Flexpen Novorapid, Flexpen Insulatard, Flexpen Levemir; **Insulclock for Flextouch (Novo Nordisk)**: Flextouch Tresiba 100, Flextouch Tresiba 200, Flextouch Fiasp

It tracks the ambient temperature, helping the patients in their decisions about the preservation of the properties of insulin, making them know at all times the temperature to which the pen connected to the device is exposed.

It facilitates the injection technique to patients with an audible warning at the end of an insulin injection, by encouraging patients to keep pressing for enough seconds for a correct administration of the medicine, according to the instructions of the manufacturer of the insulin pen.

4.2. CONTINUOUS GLUCOSE MONITORING (CGM)

The *Freestyle Libre*© continuous glucose monitoring (CGM) system is a small, disposable, and accurate sensor that does not require any capillary blood glucose calibration. The sensor automatically records glucose results every 15 minutes for 14 days without the need to carry a separate receiver or use a transmitter. Variables such as mean glycemia, time on target and glycemic variability will be analyzed with this system.

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7. OBJECTIVES

MAIN OBJECTIVE

Determine if the *Insulclock* system will improve Time in Range (TIR) compared with standard follow-up.

In a randomized controlled trial, DM1 patients with poor blood glucose control will be provided with an Insulclock device, and randomly will use the system with access to the whole information from the app Insulclock 360 and information and alarms and surveillance from the medical team through the Insulclock device and platform for endocrines, or a device in a "mute" mode, without functionality.

Hypothesis: Insulclock device and *Insulclock 360 app*, will improve TIR compared with standard insulin pens and follow-up.

SECONDARY OBJECTIVES

Objective 2: **Determine if the *Insulclock* system will improve adherence to insulin treatment compared with standard follow-up.**

Hypothesis: Insulclock device and Insulclock 360 app will improve adherence to treatment, reducing insulin omissions, dosing mistakes and mistimings compared with standard insulin pens.

Objective 3: **Determine if the Insulclock system improves glycemic control, as measured by change in HbA1c and continuous glucose monitoring (CGM) derived glucometrics, compared to the use of standard follow-up.**

Hypothesis: Insulclock device and Insulclock 360 app will improve glycemic control compared to the standard insulin pen device.

Objective 4. **Describe differences in quality of life and treatment satisfaction between patients followed with Insulclock device and Insulclock 360 app and with standard follow-up**.

The perceived satisfaction with the treatment and changes in quality of life will be evaluated at the beginning and end of the follow-up visits in patients with T1D managed with the Insulclock device in an active or "muted" mode using PROs validated questionnaires. Also, misfunctions of the system will be documented to test if the system operates properly.

Hypothesis: Insulclock device and Insulclock 360 app will improve treatment satisfaction compared to the standard follow-up.

8. INFORMATION SOURCES AND SCOPE

The trial will be carried out in:

- Endocrinology and Nutrition Unit /Diabetes Unit, Hospital General de Segovia. Segovia, Spain
- Endocrinology and Nutrition Service, Hospital de Cruces. Bilbao, Spain
- Endocrinology and Nutrition Unit, Arquitecto Marcide Hospital, Ferrol, A Coruña, Spain
- Endocrinology and Nutrition Service, Hospital Central de Asturias, Oviedo, Spain

9. TRIAL DESIGN

9.1. TYPE OF CLINICAL TRIAL

Randomized controlled open-label multicentric trial.

9.2. STUDY POPULATION CHARACTERISTICS

Type 1 diabetes patients, with insufficient glycemic control, defined as:

- HbA1c ≥ 6.5%
- and/or extreme variations (more than 1% of change in HbA1c in the last two years)
- and regular visits to the Endocrinology Unit / Diabetes Unit (more than two each year).

9.2.1 INCLUSION CRITERIA

Patients with the following criteria will be considered for the trial inclusion:

1. Age range: 14 to 80 years
2. Diagnosis of DM1
3. Patients with type 1 diabetes and poor glycemic control, defined as:
    - HbA1c ≥ 6.5%
    - and/or extreme variations (more than 1% of change in HbA1c in the last 2 years)
    - and regular visits to the Endocrinology Unit / Diabetes Unit (more than four each year).
4. Signed informed consent form
5. Ability of the subjects to use the system and fill the included questionnaires
6. Ability and willingness of following and be compatible with the protocol of the clinical trial

9.2.2. EXCLUSION CRITERIA

1. Rejection or inability to give the informed consent to participate in the trial.
2. Pregnancy or lactation
3. Addiction or abuse of alcohol, or history of drug abuse in the last years
4. Dementia diagnosis
5. Acute infection
6. Any illness or condition that, according to investigator, could interfere with the trial

9.3. DETERMINE THE SIZE OF THE POPULATION

It is planned to include the data of 80 patients with DM1 in the trial. To calculate the sample size, our previous pilot study was taken into account, to measure significant differences in TIR (time in range).

For this, we have considered the necessary number of patients to determine the mean evolution of the TIR in the population as a whole with a precision of a 30% of the variance and an alpha of 0.05. We estimate that this precision would be sufficient to demonstrate an improvement in the TIR, since 0.3 * variance is less than the mean improvement in TIR detected, and therefore we would demonstrate a relevant improvement with the use of the system.

We used the formula for the margin of error W/2:

$$W/2 = t\alpha_{/2,\ n\text{-}1} s/\sqrt{n}\ .$$

$$n = t\alpha_{/2,\ n\text{-}1}{}^2 s^2/(W/2)^2 \approx Z\alpha_{/2}{}^2 s^2/(W/2)^2 \quad \text{(with } n \approx 1{,}05 \cdot n \text{ if } n<75\text{)}$$

with the variance of the TIR obtained in the pilot study: s = 0,1414 mg/dL, therefore w/2 = 0,1414*0,3 = 0,04 mg/dL.

According to this, we need 51 participants, (26 for each arm) to demonstrate our hypothesis.

If a 30% dropout is considered, we would need 75 patients and, to add a safety margin, we will select 80 patients (40 for each arm).

10. VARIABLES AND MEASURING INSTRUMENTS

To achieve the objectives of this trial that are detailed in section 5, the following variables will be gathered:

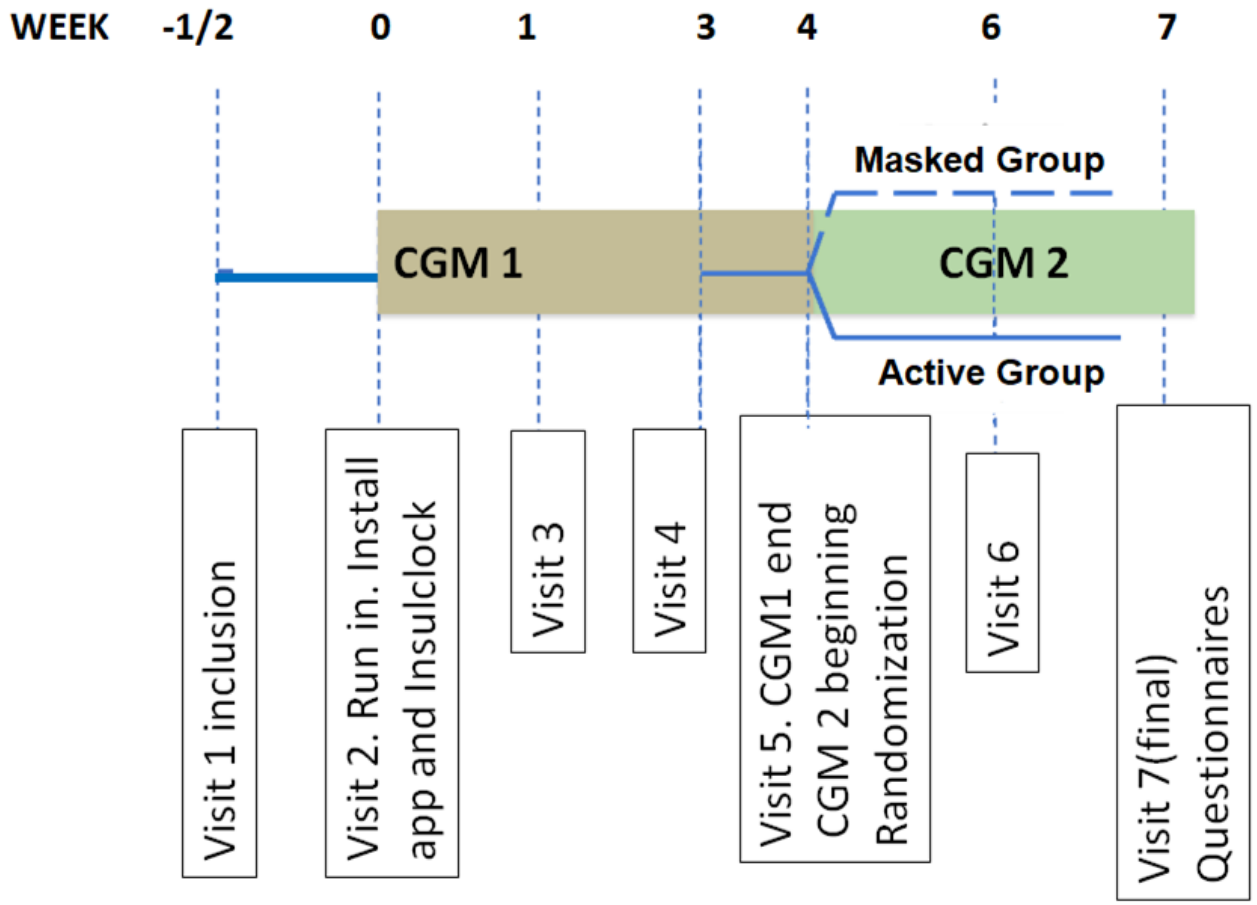
- Weight, Height, BMI
- HbA1c
- Adherence to self-analysis of capillary blood glucose
- Basal glycaemia
- Pre-prandial glycaemia
- Baseline and final HbA1c
- Continuous glucose monitoring (CGM) derived glucometrics: average glycaemia, time in range and glycemic variability.
- Timing, dose and fulfillment of insulin dosing.
- Treatment satisfaction will be assessed with the questionnaire (DTSQ) and with the Insulin Treatment Satisfaction Questionnaire (ITSQ), both validated (ref 28-30). They will be provided at the randomization (visit 2, week 0) and in the final visit (5) to assess relative changes in DTSQ between interventions. Differences in scores of DTSQc indicate the differences in satisfaction, while the direction (positive or negative) indicates which therapy is preferred.

11. PROTOCOL DESCRIPTION

This trial will be randomized (1:1), controlled, open-label multicenter with patients with DM1 with insufficient glycemic control, defined as:

- HbA1c ≥ 6.5%
- and/or extreme variations (more than 1% change in HbA1c within the last 2 years)
- and regular visits to the Endocrinology Unit / Diabetes Unit (more than 2 per year).

11.1. DESIGN



11.2.TRIAL DURATION

The duration of this study will include a 1-week run-in and a 7-week follow-up phase.

11.3.PATIENTS SELECTION. NUMBER OF EXPECTED SUBJECTS.

The total number of patients with DM1 to be included in this trial is 80.

Attrition rate of 30% is anticipated through week 6, due to a 20% drop-out during screening phase and a 10% drop-out during run-up phase.

11.4.METHODS: STUDY VISITS

SCREENING (VISIT 1) (WEEK -1/-2)

1/2 weeks prior to the start of the study, all potential study patients will be screened for eligibility after signing the informed consent form (ICF) and will be assigned with a patient identification number.

- Clinical history, physical examination, height, weight, vital signs, pre-existing conditions, and concomitant medications will be recorded during this visit.
- Laboratory evaluations (HbA1c, serum chemistry) must be available within the last 2 months.
- Patients who do not meet all the inclusion criteria at visit 1 will be considered screen failures and will not be included to participate in the study.
- An identification number will be assigned to each participant.

RUN-IN (VISIT 2) (WEEK 0)

- Patients will receive detailed instruction on the installation and use of Insulclock device and app on masked mode.
    - *If the patient does not use a CGM:* a healthcare professional applies the *FreeStyle Libre Pro* sensor to the back of the upper arm and activates it.
    - *If the patient already uses a CGM system,* the patient will be encouraged to use sensors during this period.
- Telephone assistance will be offered during the trial.
- Patients will be assisted to link the Insulclock device to the mobile application and will be instructed on the correct use of the FreeStyle Libre.

FIRST VISIT CGM 1 (VISIT 3) (WEEK 1)

- Patients will be encouraged to use the system

FOLLOW-UP. VISIT 4. (WEEK 3)

- Patients will be encouraged to use the system

VISIT STARTING CGM 2 AND RANDOMIZATION (VISIT 5) (WEEK 4)

Randomization: Patients are assigned to a group

Patients in Insulclock Active mode Group:

- Patients will receive detailed instructions on using the Insulclock 360 app and Insulclock device.
- They will be instructed and motivated for full use of all system functions: alarms, messages to the caregivers and investigation team.

Patients in Insulclock Masked mode Group:

- Patients will be instructed on the correct installation and use of the masked Insulclock device and Insulclock app for recording insulin bolus information.
- They do not receive any other information and will not have access to the Insulclock 360 application from the Internet.
- They will keep administering insulin treatment as before.

Second CGM:

- *If the patient does not use a CGM:* a healthcare professional applies the *FreeStyle Libre Pro* sensor to the back of the upper arm and activates it.
- *If the patient already uses a CGM system,* the patient will be encouraged to keep using the sensors during this period.

- Mobile application diaries will be reviewed for checking glucose levels, hypoglycemic episodes, self-administered insulin

FINAL VISIT CGM 2 (VISIT 6) (WEEK 6)

- Patients will be encouraged to use the system

FINAL VISIT (VISIT 7) (WEEK 7)

- Mobile application diaries will be reviewed.
- The questionnaires on quality of life and satisfaction with treatment will be delivered for patients to fill out: DTSQ and ITSQ

12. STATISTICAL ANALYSIS

12.1. INTRODUCTION AND GENERALITIES.

The proposed statistical analysis methods shown below constitute a synthesis of the methods to be used in this study to apply them to the data collected and respond to the general objective and the specific objectives.

Data from all patients included in the study, who meet the selection criteria, will be analyzed. Data in absentia will not be charged and will be considered as lost.

A general description of the variables included in the study will be made. The absolute and relative frequency distributions of the qualitative variables will be presented, as well as the measures of central tendency and dispersion (mean, standard deviation, median, minimum and maximum) of the quantitative variables. The confidence intervals will be presented at 95% for the main quantitative outcome variables associated with the main objective and the main secondary variables.

12.2. STATISTICAL ANALYSIS

The data corresponding to the variables included in the main objective will be descriptively analyzed.

The SPSS software Version 17.0. will be used to perform the analysis. The hypothesis tests that are carried out will be in all bilateral cases and with a significance level of 0.05. For variables that do not fit the normal distribution (or parametric), the Mann Whitney hypothesis tests will be used (for unpaired data). The chi-square test (or Fischer's exact test when appropriate) will be used for the analysis of contingency tables as well as for the comparison of proportions and/or frequency distributions.

13. ETHICAL ASPECTS

13.1. GENERAL CONSIDERATIONS

The study will be carried out in accordance with the requirements expressed in the international standards relating to conduct epidemiological studies, included in the International Guidelines for Ethical Review of Epidemiological Studies (Council for the International Organizations of Medical Sciences –CIOMS-, Geneva, 1991), as well as the Declaration of Helsinki (Tokyo revision, October 2004). The latter defines the principles that must be scrupulously respected by all the people involved in the investigation.

The processing, communication and transfer of personal data of all patients will comply with the provisions of the Spanish Ley Orgánica 3/2018, de 5 de diciembre, de Personal Data Protection and guarantee of digital rights.

13.2. BENEFIT-RISK ASSESSMENT

Potential risks to subjects

The Insulclock device and Insulclock 360 app have no known health risks. The present study has no possibility of generating any risk for the patients studied as it does not imply any change in the treatment or in the diagnostic procedures that the patient would undergo under conditions of routine clinical follow-up.

Benefits for included subjects

Closer follow-up should turn into improved glycemic control.

The benefits of using the device should be seen in the patients using it in active mode.

13.3.INFORMATION SHEET AND CONSENT FORM

Informed Consent of patients will be obtained by delivering the "Patient Information Sheet" (Annexed 2).

The researcher responsible for the study will inform the patients, answer their doubts and questions, and in accordance with current regulations, obtain the patient's consent.

The patient participating in the study may revoke his/her consent for the use of his/her data in the analysis at any time, without justifying his decision, and without any liability or damage arising for him/her.

13.4.CONFIDENTIALITY OF DATA

In order to guarantee the confidentiality of the study data, only the researcher and his team of collaborators, the Clinical Research Ethics Committee and the relevant health authorities will have access to them.

The data of the researcher and the study will be entered and processed in accordance with the provisions of Spanish Organic Law 3/2018, of December 5th, on Personal Data Protection and guarantee of digital rights, exclusively for the development and proper end of the study.

13.5.INTERFERENCE WITH PHYSICIAN'S PRESCRIBING HABITS

The project proposed here does not interfere in any case with treatment habits, since it is limited to collecting data from patients in which the doctor has already defined the type of treatment to be used to treat the patient.

14. PRACTICAL CONSIDERATIONS

14.1.WORK PLAN

The trial will be developed by filling in a questionnaire that collects all the necessary information available in the clinical history.

In no case will the information collected include data that allows knowing the identity of the patient.

14.2.FINAL AND FOLLOW-UP REPORTS

After the closure of the study, the statistical analysis will be carried out. A copy of it will be sent to the Clinical Research Ethics Committee.

14.3.PUBLICATION CONDITIONS

Regarding the conditions of communication and publication of results, the established rules will be observed:

1. The publication of this clinical trial will be carried out in scientific journals and with mention of the Clinical Research Ethics Committees to which the study has been submitted for approval.
2. The anonymity of the cases included in the study will be maintained at all times.
3. The results or conclusions of this clinical trial will be communicated as a priority in scientific publications before being disclosed to the non-healthcare public.

14.4.RESPONSIBILITIES OF THE PRINCIPAL INVESTIGATOR

The responsibilities of the study principal investigator are:

- ✔ Sign the protocol and any modification.
- ✔ Take responsibility for the preparation of the final report.
- ✔ Disseminate the results of the clinical trial.

14.5.RESPONSIBILITIES OF THE SITE INVESTIGATORS

The responsibilities of the sub-investigator will be:

- ✔ Sign a commitment in which the investigator recognizes himself as a study researcher, affirms that the investigator knows the protocol and agrees with it in all its terms.
- ✔ Inform the research subjects and obtain their consent.
- ✔ Guarantee that in any case the confidentiality of any information about the cases studied will be respected.
- ✔ Collect, record and report data correctly.
- ✔ Send the corresponding information within the established deadlines and through the indicated means.
- ✔ Facilitate audits and inspections of health entities.
- ✔ Know how to respond before the scientific and professional community about the objectives, basic methodology and meaning of the study results.

Annexed 1. Clinical Research Ethics Committee Approval

It will be attached in a separate document.

Annexed 2. Patient information sheet

Title: Randomized clinical trial to assess the efficacy of the system Insulclock® for insulin treatment management with type 1 diabetes patients with insufficient glycemic control

Principal Investigator: Dr. _____

Version Date: January 9th, 2021

To be completed by the doctor:

Doctor name: _____
Telephone number: _____

Please read this information sheet carefully:

Trial Title: Randomized clinical trial to assess the efficacy of the system Insulclock® for insulin treatment management with type 1 diabetes patients with insufficient glycemic control

You are currently being invited to participate in a study whose objective is to collect data on the possible usefulness of a device to assist in the management of insulin treatment.

To know if you want to participate in this study, you should understand why the project is going to be carried out and what it consists of. Please take as much time as you need to read this information carefully and discuss as much as you like with your doctor, your friends and your family. Tell your doctor if you want more information and ask him all your questions. Also, have enough time to decide whether or not you want to participate.

What is the purpose of this project?

The purpose of this study is to determine whether the Insulclock device will improve adherence to therapy by reducing insulin missing doses, dosing errors, and injection timing compared to the standard pen device.

Insulclock® [27] is a small electronic device that connects to all insulin pen devices and allows information to be tracked on date, time, last injection dose, remaining insulin in the pen device, as well as type of insulin used and the temperature. Insulclock® has an alarm / reminder system with visual and acoustic alerts to reduce insulin omissions and dosing and injection timing errors. Via Bluetooth and smartphone technology, the information is stored and available for analysis by patients, caregivers and healthcare professionals.

It is a randomized controlled study: This means that half of the cases will use the device in blind mode (without information about it) and the other half will have access to the information it registers and its alarms.

Why have I been selected?

We talk to you because you were once diagnosed with Type 1 Diabetes Mellitus and you may be an ideal candidate to provide information about your disease.

Like you, it is planned to invite approximately 60 patients to participate in this study.

What will happen to me if I participate?

If you decide to participate, your doctor will review your medical history, including tests that have been performed to diagnose your disease. During the trial, you will be asked to fill in simple questionnaires about your quality of life and your treatment. You will also be fitted with a small, disposable, and accurate sensor that does not require any capillary blood glucose calibration. Sensor automatically records (blind to patient) glucose

results every 15 minutes for 14 days. Variables such as mean glycemia, time to target and glycemic variability will be analyzed with this system.

Who will participate in the study?

As mentioned before, the study is scheduled to take place in your hospital, where doctors treat and follow up patients with the same disease. Approximately 60 patients are expected to participate by providing their data for this study.

Do I necessarily have to participate?

You are free to decide whether or not you want to take part in this study. If you decide to participate and for any reason change your mind, you can tell your doctor at any time. Your decision will not affect the quality of health care you receive now or later.

What are the possible benefits of my participation in the study?

Closer follow-up during the 6 weeks as well as the results of the 2-week continuous glucose monitoring should translate into improved glycemic control. The benefits of using the device should be seen in patients using them in active mode.

In addition, the information and conclusions derived from it may help increase knowledge about the most indicated treatments for patients suffering from their disease. This information could benefit other people in the future, who like you, fight against this same type of disease.

Will the confidentiality of my participation in the study be respected?

Your name will not be known in any case.

If you decide to take part in this study, you will be asked to sign a written consent form..

During this study, data about you and your illness will be collected. These data will be handled in accordance with the Spanish Organic Law 3/2018, of December 5th, on Personal Data Protection and guarantee of digital rights. You have the rights that the aforementioned law recognizes. Your data will be collected by your doctor and sent so that those responsible for the study or other people acting on their behalf, can study and analyze them.

By agreeing to participate in this study, you consent to the collection, processing, assignment and transfer (if applicable) of the data related to this study, with total guarantee of anonymity.

According to current law, patients have the right to access their personal data and can exercise the right of access, information, rectification, deletion and oblivion, limitation of processing, opposition, portability and not to be the subject of automated individual decisions. You can do this by asking the doctor who is inviting you to participate in the study.

All information about you related to your participation in the study will be treated with the strictest confidentiality and will only be disclosed to medical experts for scientific evaluation. You will be identified only by a number.

Your data, as well as information about your general health and the answers to the questions asked, will be analyzed and the results could be used in scientific presentations or publications and used in future medical research.

Contacts for more information

If you have any questions regarding the study, consult your doctor.

Annexed 3. Informed Consent Form

Written Informed Consent Form for Adults

Title: Randomized clinical trial to assess the efficacy of the system Insulclock® for insulin treatment management with type 1 diabetes patients with insufficient glycemic control

Principal Investigator: Dr,

Version Date: January 9th, 2021

I, (name and surname)_____.

I have read the information sheet on the Randomized clinical trial to assess the efficacy of the system Insulclock® for insulin treatment management with type 1 diabetes patients with insufficient glycemic control.

I have been able to ask questions about the study.

I have received enough information about the study.

I have talked with the doctor_____.

I understand that my participation is voluntary.

I understand that I can withdraw from the study:

- whenever I want
- without having to give explanations
- without this affecting my medical care

I understand that by agreeing to participate in this study, I consent to the collection, processing, assignment and transfer (if applicable) of my personal data with respect to anonymity for health care and / or medical research purposes.

I freely give my consent to participate in the study and that my data can be used for research purposes. I will receive a signed copy of this patient information sheet and informed consent.

Patient signature: Date:_____/_____/_____

Investigator signature: Date:_____/_____/_____

Written Informed Consent Form for Adults for under 18s

Title: Randomized clinical trial to assess the efficacy of the system Insulclock® for insulin treatment management with type 1 diabetes patients with insufficient glycemic control

Principal Investigator: Dr, _____

Version Date: January 9th, 2021

I, (name and surname)_____.

I have read the information sheet on the Randomized clinical trial to assess the efficacy of the system Insulclock® for insulin treatment management with type 1 diabetes patients with insufficient glycemic control.

I have been able to ask questions about the study.

I have received enough information about the study.

I have talked with the doctor_____.

I understand that my participation is voluntary.

I understand that I can withdraw from the study:

- whenever I want
- without having to give explanations
- without this affecting my medical care

I understand that by agreeing to participate in this study, I consent to the collection, processing, assignment and transfer (if applicable) of my personal data with respect to anonymity for health care and / or medical research purposes. After we have explained in an understandable way for his/her age the protocol, benefits and risks to my child or legal representative, I freely give my consent for them to participate in the study and that their data can be used for research purposes. I will receive a signed copy of this patient information sheet and informed consent.

Patient signature: Date: / /

Parent's signature Date:_____/_____/_____

or legal representative of the patient

Investigator signature: Date:_____/_____/_____