Overview Page

Study name	Comparative effectiveness of point-of-care glycosylated hemoglobin measurement (POC-A1c), vs. the current standard based on oral glucose tolerance test, for the early detection of Diabetes Mellitus type 2 (DM2) in Colombia. **EDDIT-1 STUDY**
Protocol Identification Number	CGIS-DM-001-18
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List of abbreviations:

- ADA: American Diabetes Association
- **CLIA**: Clinical Laboratory Improvement Amendments
- **DANE**: National Administrative Department of Statistics
- **DCCT**: Diabetes Control and Complications Trial
- **DM2**: Type 2 Diabetes Mellitus
- **FINDRISC**: Risk model for diabetes mellitus in Finnish population
- **GAA**: Impaired Fasting Glucose
- **GB**: Basal glycemia
- **GPC**: Clinical Practice Guidelines
- **GI**: Glucose intolerance
- **NGSP**: Glycosylated Hemoglobin Standardization Program
- **WHO**: World Health Organization
- **POC-A1c**: Measurement of glycosylated hemoglobin at the point of care
- **OGTT**: Oral Glucose Tolerance Test

Protocol Synopsis

Title	Comparative effectiveness of point-of-care glycosylated hemoglobin measurement (POC-A1c), vs. the current standard based on oral glucose tolerance test, for the early detection of Type 2 Diabetes Mellitus (T2DM) in Colombia. **EDDIT-1 STUDY**
Purpose and justification	In order to significantly increase the early detection of patients with T2DM, it is necessary to explore alternative strategies for actively searching for patients with prediabetes or undiagnosed diabetes. These alternatives may include taking a screening questionnaire and a point-of-care test to improve the proportion of patients attending a confirmatory test. The objective of this study is to evaluate the impact of such a strategy.
Objectives	In patients at risk identified by FINDRISC (i.e., score greater than or equal to 12), determine the difference in the number of patients who attend a confirmatory test (GTT) after the isolated application of the screening questionnaire versus the completion of the supplemented questionnaire by POC-A1c.
Study design	Prospective, open label, randomized, controlled study.
Population	Adult patients with no known diagnosis of diabetes
Inclusion criteria	• Adult, aged over or equal to 18 years and less than or equal to 75 years. • Understand, accept, and sign informed consent • FINDRISC greater than or equal to 12
Exclusion criteria	• Previous diagnosis of type 1 or type 2 diabetes mellitus • Pregnancy or lactation at the time of inclusion in the study (referred by the subject). • History of cancer in the subject (must be in remission for 5 years) • Known history of familial hyperlipidemia. • Chronic use of systemic corticosteroids (Defined as: a dose greater than 5 mg of oral prednisolone or its equivalent and / or consumption greater than one month thereof). • Known history of hemophilia or other bleeding disorders • Known history of stage IV or V chronic kidney disease • Known history of HIV (on antiretroviral therapy) • History of sickle cell disease • Known history of glucose 6 phosphate dehydrogenase deficiency • Known history of blood transfusion in the past 3 months • Known history of erythropoietin therapy in the past 6 months.
Duration of the study	Each subject will participate in the study approximately 4 months, in addition, each patient will be given a follow-up call 30 days and 90 days from the date of inclusion in the study.

Procedures	The doctor explains what the study consists of and obtains informed consent. If the patient accepts, the FINDRISC will be verified, the inclusion and exclusion criteria are verified and the relevant data from their medical history will be recorded. Subsequently, the subjects will be included in the study and randomized into two groups. In the participants of group A (intervention) they will be offered information on healthy lifestyles according to their result in the FINDRISC questionnaire and then a measurement of POC-A1c. In the participants of group B (control) they will be offered the same information on healthy lifestyles according to their FINDRISC result. In addition, all randomized participants will be invited to perform a GPOT in the allied work of CAIMED or in the laboratory of their choice with the necessary preparation recommendations for the realization of the same. For this purpose, they will be given an order that includes the date of screening, a tracking number and time window in which they must go (i.e., 30 days and with a second attempt-maximum window at 90 days). After 30 days from the delivery of the order for the PGTO, a call will be made to the randomized subjects to check if the exam was taken and its result requested in case it has done so, if the examination, you must send it to the center. Otherwise, the causes of not having made the previously recommended GTT will be investigated, and a new call will be made after 90 days. In patients who, if they attended the performance of the OGTT and obtained a presumptive result of diabetes (defined as an impaired oral glucose tolerance test and/or impaired POCA1C test according to the ADA guidelines), a closing call will be made 30 days after the test was done to confirm if they started to control their disease. For this, it will be instructed to attend consultation by general medicine according to what is contemplated by its entity administering benefit plans, ending the follow-up.
Analysis plan	For the primary objectives, the proportion of patients who attended the performance of the PGTT in each of the groups will be obtained and the statistical significance test for superiority in the follow-up ratio of the intervention group (A) over the control group (B) will be applied. Additionally, descriptive statistics will be obtained regarding the dynamics of application of the confirmatory test (i.e., latency time).
Security monitoring and assessments	For the application of the FINDRISC screening questionnaire it is required to take non-invasive anthropometric measurements and to establish the status of prediabetes or undiagnosed diabetes, blood samples are required. The safety follow-up to these procedures will be carried out in accordance with current standards.

Title

Comparative effectiveness of point-of-care glycosylated hemoglobin measurement (POC-A1c), vs. the current standard based on oral glucose tolerance test , for the early detection of Type 2 Diabetes Mellitus (T2DM) in Colombia. **EDDIT-1 STUDY**

Theoretical framework

Type 2 diabetes mellitus (T2DM) is a growing public health problem in the world and in Colombia. In 2020, this pathology was considered the ninth cause of mortality in the world according to the global burden of disease (GBD) with more than 1 million deaths per year directly caused by diabetes (1). In Latin America, 1 in 3 adults living with diabetes are undiagnosed and in Colombia the behavior is similar, as reports from the High-Cost Account indicate that 3 out of every 100 Colombians have diabetes mellitus. However, the Ministry of Health and Social Protection estimates that the number is much higher and one in 10 people in Colombia suffers from this disease, this because at least half of the population does not know they have this pathology.

To reduce the gap of undiagnosed people, it is necessary to design and implement strategies for early detection of T2DM. The Berlin Declaration (2), published in October 2016 and supported by the IDF as well as other organizations, has identified early detection as a priority line and has set a goal for achieving this priority (2). This statement proposes to increase by 50% the number of people taking a risk test for T2DM and by 50% the number of high-risk people receiving a diagnostic test for T2DM.

According to this, it is important to consider the diagnostic criteria set forth by the American Diabetes Association (ADA) in 2022 (3):

- Fasting blood glucose (fasting - absence of caloric intake for at least 8 continuous hours) ≥ 126 mg/dL

or

- Oral Glucose Tolerance Test (according to WHO guidelines with an equivalent of 75 g of anhydrous glucose dissolved in water) at 2 hours: ≥ 200 mg/dL

or

- HBA1C ≥ 6.5%

or

- In patients with classic symptoms of hyperglycaemia or hyperglycaemia crisis, or random glycaemia ≥ 200 mg/dL

*Note: To make the definitive diagnosis, it is necessary to perform two tests (the same or different) and that both are impaired.

Likewise, itdefines as pre-diabetes, those patients who have impaired values of plasma glycemia as follows:

- Fasting plasma blood glucose: 100-125 mg/dL or

- Plasma glycaemia between 144-199 mg/dL 2 hours post OGTT

or

- HbA1c between 5.7% to 6.4%

In this way, and in accordance with the guidelines of the Colombian Clinical Practice Guidelines, an adequate and timely approach to the patient suffering from this disease avoiding serious long-term outcomes.

Background for the protocol

The risk score to predict the occurrence of DM2 was developed based on a prospective follow-up record conducted after a baseline survey from a census sample Finland's national of 4,450 subjects aged 34-74 years followed over 10 years. The validity,

specificity and predictive power of the risk score was initially assessed, both with cross-sectional data from the study and by comparing the scores with the results of the oral glucose tolerance study conducted on the same people. It was also validated with another population survey with a prospective five-year follow-up. The findings confirmed the high specificity and low false positive rate of the risk score for probability of development of DM2 (4).

As for the measurement of glycaemic levels, although a recent review by Barry et al. points out that screening with glycosylated hemoglobin (A1c) and basal glycaemia is imprecise (5), it is clear that in the Cases that are detected early, interventions can be made that prevent or delay the onset of diabetes and its complications. For their part, Barengo and Tuomilehto point out the importance of early detection of prediabetic patients with post-load glucose intolerance, to induce lifestyle changes that prevent the progression to diabetes (6).

Finally, the Clinical Practice Guide (CPG) of DM2 published in Colombia by the Ministry of Health cites the study of Simmons and collaborators which shows that the subjects who were invited and attended to the invitation to perform the screening between 1990 and 1992 had alower morbidity compared to subjects who did not undergo screening (6). On the other hand, subjects who were invited to perform the screening test but did not heed the invitation showed significantly higher mortality (6).

Description of the products used

Today there is availability of equipment that performs the measurement of glycosylated hemoglobin at the point of care (POC-A1c) and that meets the standards proposed by the "National Glycohemoglobin Standardization Program" (NGSP) and the "Diabetes Control and Complications" Trial" (DCCT). This equipment can perform POC-A1c tests in contexts outside of central laboratories, although in the United States it is only authorized to be used in contexts of "Moderate Complexity" according to the classification of "Clinical Laboratory Improvement Amendments" (CLIA).

The personnel who handle the equipment must be trained and the environmental conditions for its correct operation are predefined by the equipment in such a way that they do not operate if these conditions are not met. The restriction of equipment to environments of moderate complexity is applicable only to the United States, but in derived contexts equipment performing point-of-care testing offers a great opportunity to make immediate diagnoses without losing patients, as demonstrated by sub-Saharan Africa's experience in HIV detection and the immediate onset of HIV screening treatment (7).

The laboratory where the Oral Glucose Tolerance Test (OGTT) is performed must comply with the standardized recommendations for the collection of samples according to local regulations and guarantee the equipment and packages available in the country.

Purpose and justification

With the aim of increasing the number of people detected early with DM2, it is currently recommended as an initial screening tool, the application of the FINDRISC questionnaire, in Colombia this questionnaire counts with validation studies demonstrating significant sensitivity and specificity when predicting diabetes (8). If that questionnaire yields a score greater than or equal to 12, a diagnostic test for DM2 should be performed. GPC considers three diagnostic tests: basal glycemia (GB), oral glucose tolerance test (OGPT), and glycosylated hemoglobin (A1c). Each test of these has advantages and disadvantages as well as their respective sensitivity and specificity, according to this, the economic evaluation of the different alternatives allows us to conclude that the recommended strategy is FINDRISC plus GB and OGTT (6)

The economic evaluation of the CPG estimated the costs and benefits based on a decision tree that assumes that all individuals detected at risk in FINDRISC are subsequently tested. However, this assumption is questionable because the performance of a complementary test implies that the patient has to go to a site de taking samples on an empty stomach, which generates barriers derived from the time and money that this requires. Additionally, there are other barriers such as the difficulty of fasting and the process of taking the sample itself. Overall, it is reasonable to propose that the proportion of patients completing the process is less than 100%.

If it is assumed that the loss of follow-up to patients is not trivial, an alternative confirmation strategy must be designed to reduce this loss. One possibility is to perform an A1c test at the very moment the patient answers the FINDRISC questionnaire and is classified as a patient at risk. La GPC does not explicitly consider performing point-of-care A1c testing (POC-A1c) and refers to performing it in a centralized laboratory.

As noted above, in resource-limited contexts, point-of-care testing teams enable immediate diagnoses without losing patients, as demonstrated by sub-Saharan Africa's experience in HIV detection and immediate initiation of treatment (7).

One disadvantage that has been pointed out about point-of-care testing is that its unit cost is higher compared to tests performed in a processing center. However, this agreement only considers the direct cost of the test and does not know the impact that the immediate diagnosis generates on other costs, such as the need for successive consultations and the avoidable morbidity that occurs because of the loss of follow-up to the patient.

Additionally, to make point-of-care testing affordable, it is necessary to design and implement an operating model that is very different from the traditional central laboratory model, for this, it is necessary to contemplate the screening of populations that go to other health services in those that have been identified as having an increased risk. For example, it has been documented that periodontal disease is associated with diabetes so that in adults over 30 years of age who attend general dentistry consultations, up to 30% patients with alterations of the glycemic profile can be found (9).

In this frame of reference, it is proposed that to significantly increase the early detection of patients with DM2 it is necessary to explore alternatives for active search for patients with prediabetes or undiagnosed diabetes. These alternatives may include the completion of a screening questionnaire and a confirmatory test at the point of care, however, to achieve a higher rate of early detection it is necessary to find a balance between adequate sensitivity and specificity with less loss of follow-up.

Primary objectives

- In patients at risk identified by FINDRISC (i.e., score greater than or equal to 12), determine the difference in the number of patients attending a confirmatory test (GTT) after the isolated application of the screening questionnaire versus the completion of the questionnaire supplemented by POC-A1c.

Secondary objectives

- To determine the probability of attending a confirmatory test (GTT) for DM2, in the population at risk identified by FINDRISC.
- To determine the probability of attending a confirmatory test (GTT) for DM2, in the risk population identified by FINDRISC in whom POC-A1c was applied.
- Determine the performance in terms of time and adherence of the application of POC-A1c against the current recommendations in the GPC (ADA).
- Describe the causes of non-performance of the confirmatory test and identification of predictors of non-performance or postponement of the diagnostic test within a maximum period of 90 days from the initial recommendation.

Study design

Overview

Study, prospective, open, randomized, controlled.

Justification of the main elements of the protocol

The FINDRISC screening questionnaire has been previously studied and validated, can be applied quickly, economically and its low complexity makes them widely available (5,10). Similarly, previous studies have shown that periodontal disease is related to the appearance of alterations in the glycemic profile so that up to 30% of adults over 30 years of age who attend general dentistry consultations are identified as a population at risk (3).

Despite the drawbacks to its mass application, OGTT remains included within the current CPGs and continues to be a reference test for the diagnosis of patients with DM2 (3).

Measurement of A1c may be more convenient than OGTT, particularly if performed at the point of care (POC-A1c). Additionally, the characteristics for its implementation and its technical profile are clearly established. However, its impact on the screening algorithm under real conditions of use is unknown and its profile for inclusion within a mass screening system has not yet been established.

Setting the primary endpoint

While it is possible to perform screening using any of the validated questionnaires, in real conditions of their implementation a second visit of the patient is required to perform a confirmatory test (GTT) and the loss to follow-up isrequired a major challenge for health systems. It is proposed that the implementation of POC-A1c can contribute to improving the follow-up rate in the context of population screening and facilitate the successful implementation of large-scale screening campaigns.

Therefore, the primary outcome is the probability of going to OGTT according to the strategy implemented.

Choice of comparator

Currently, the screening guidelines contemplate the completion of the FINDRISC questionnaire followed by a confirmatory test carried out in the centralized laboratory. Because of this, the recommended practice is established as a comparator.

Type of design

Prospective, open label, randomized, controlled study in adults with no known diagnosis of diabetes.

Study procedures

A Pre-Screening activity will be carried out, with prior authorization of use of personal data, where the FINDRISC test will be applied to different population groups and in case the subjects obtain 12 points or more, they will be invited to participate in the study. Otherwise, participants with 11 points or less according to the application of FINDRISC will receive brief information on healthy lifestyles according to their risk group, ending the activity.

Once the Pre-Screening activity has been carried out, to carry out each day, a work site will be installed in the different places established to carry out the screening of the disease that will be attended by a doctor, bacteriologist, and nursing assistant. Subjects at risk identified by FINDRISC will be explainedwhat the study consists of; if they wish to participate in it, and understand, accept, and sign the informed consent: the doctor will proceed to record the relevant data in their medical record, evaluate inclusion and exclusion criteria.

Subsequently, the participants will be randomized into 2 groups. Participants in group A (intervention) will be offered information on healthy lifestyles according to their outcome and will be given a measurement of POC-A1c*. In the participants of group B (control) they will be offered the same information on healthy lifestyles according to their FINDRISC result.

**The work site will have a properly covered cubicle, in which a POC-A1c equipment will be available with the necessary requirements of location and operation to guarantee the validity of the test. In this cubicle will be a laboratory assistant who executes the pre-analytical and post-analytical phase.*

In addition, all randomized participants will be invited to perform a GPOT in the CAIMED partner laboratory or in the laboratory of their choice with the preparation recommendations necessary for the realization of the same. For this purpose, they will be given an order that includes the date of screening, a tracking number and time window in which they must go (i.e., 30 days and with a second attempt-maximum window to 90 days).

After 30 days from the application of the screening, a call will be made to the randomized subjects to check if they performed the indicated diagnostic test and the result of the OGTT, if the examination has been carried out, must be sent to the center (either by scanning, photographing, or bringing it to the research center). Otherwise, the causes of non-realization of the same will be investigated and a new call will be made after 90 days. In patients who, if they attended the performance of the OGTT and obtained a presumptive result of diabetes, a closing call will be made 30 days after the test was performed to confirm if they began control of their disease. For this, you will be instructed to attend a consultation by general medicine according to what is contemplated by your entity administering benefit plans, ending the follow-up.

Study population

Adult patients with no known diagnosis of diabetes attending a health care facility.

Inclusion criteria

- Adult, aged 18 years or older and under or equal to 75 years old
- Understand, accept, and sign informed consent
- FINDRISC greater than or equal to 12

Exclusion criteria

- Previous diagnosis of type 1 or type 2 diabetes mellitus
- Pregnancy or lactation at the time of inclusion in the study (referred by the subject)
- History of cancer in the subject (must be in remission for 5 years)
- Known history of familial hyperlipidemia
- Chronic use of systemic corticosteroids (Defined as: a dose greater than 5 mg of oral prednisolone or its equivalent and/or consumption greater than one month thereof).
- Known history of hemophilia or other bleeding disorders
- Known history of stage IV or V chronic kidney disease
- Known history of HIV
- Known history of sickle cell disease
- Known history of 6 phosphate dehydrogenase deficiency
- Known history of blood transfusion in the past 3 months
- Known history of erythropoietin therapy in the past 6 months.

Criteria and procedures for the withdrawal or suspension of subjects

Type and time of data collection corresponding to withdrawn subjects

The subject who decides to participate in the study can choose to withdraw at any time, since no therapeutic interventions are being applied, only guidance will be offered to the subject regarding their risk condition as has been established until that moment of the study and the moment in that its follow-up is terminated.

Whether to replace subjects and how

Withdrawn subjects will not be replaced.

Follow-up of withdrawn subjects

Once the subject expresses his intention to withdraw, the follow-up will be terminated.

Criteria for the interruption of the study.

Since the intervention is not therapeutic and the technical conditions for performing laboratory tests are standardized, no a priori termination criteria are established.

Interventions

Description of interventions

The FINDRISC (applied in Pre-Screening activity) will be verified; for this it is necessary to take anthropometricas well as non-invasive measurements. Additionally, to establish the diagnosis of prediabetes or undiagnosed diabetes, invasive activities such as blood sampling are required.

Non-invasive measurements

Body weight (at 0.1 g precision) in lightweight underwear, without footwear, will be recorded at the screening visit as well as height (at 0.5 cm precision), that is, both measurements will be obtained at the beginning of the study. The waist and hip circumference will be taken twice, then the average of both measurements will be made.

Biochemical measurements

The PGTT will be carried out according to the standards of the allied laboratory or of preference by the patient, and under the local regulations of the country with the recommendations of the WHO. Ideally, the loading solution should contain 75 g of anhydride glucose and 1.6 g of citric acid, the first sample of glycemia will be obtained after 8 - 12 hours of fasting and the second sample will be obtained 2 hours after glucose loading. All this according to the recommendations described by the WHO.

PoC-A1c will be measured at the screening site using validated equipment that complies with international standards. Kits and processing methods will be ensured to be certified by the NGSP and standardized with the DCCT assay. The POC-A1c test shall be considered impaired for any value equal to or greater than 5.7% (3).

Enumeration of the participant

The enumeration of patients will be sequential since it is performed in a single center.

Allocation of the intervention

Once the participant has accepted and signed the informed consent, the doctor will verify the FINDRISC questionnaire previously applied in prescreening activities), as well as inclusion and exclusion criteria and random assignment will be carried out by the research team.

The random allocation sequence will be automatically generated through the platform intended for this purpose. A member of the research team will record the group to which the participant was assigned on the data logging platform.

Instructions to the patient

In Pre-Screening activities, a member of the research team must give the participant a flyer with educational information about healthy lifestyles, regardless of the participant's score. In addition to all participants who enter the study, they will be given an order for the realization of the PWG with the relevant indications for the taking of the sample and the flyer mentioned above.

In this documentation must be the sequence number that was assigned to the patient, as well as their identification number so that when they go to the sampling site (CAIMED allied laboratory/Laboratory of their preference) they are identified as a participant in the study. This will make it possible to monitor which participants have already completed the GGP. 30 days after applying the screening questionnaire or the completion of the GTT, the follow-up call is made.

The script is as follows:

> "Good morning / good afternoon / good evening, Madam/Sir (name of the subject). My name is (Contributor Name) I am (Position) We are calling you on behalf of the diabetes early detection study. As you recall, on the day (date

of inclusion in the study) you participated in the site (inclusion site to the study) in the diabetes study. I would like to know if you had the sugar test indicated by the doctor (corresponding to the day of completion of window 1 for the OGTT).

(Wait for a reply)

If the patient replies that the test was performed, the date and result should be confirmed and ask: "Could you please send us a photo or any proof of the report? Finally, the call should end like this: "Thank you very much Ms./Mr. (name of the subject). Remember to consult your doctor or your EPS to initiate timely management of the disease (in case it is impaired) or monitor the risk at least annually."

If the answer is I have not taken the test: Could you please tell us why you have not taken the sugar test? Wait for a response, and document it, end the call like this: "Remember that we will call you in 2 months again to confirm if the test was done."

**The answers are recorded by the platform and will be analyzed qualitatively by the researchers.*

Scheduling of study visits (schedule)

Responsible	**Prescreening**	**Visit 1**	**Phone Call 1 (30 days ± 3 days)**	**Phone Call 2 (90 days ± 3 days)**	**Phone Call 3 (30 days after reporting to the center ± 3 days, if applicable)**
Doctor – Bacteriologist – Research Assistant	Conferences of application of FindRisc as risk screening				
Doctor		Explanation of the study, its procedures and obtaining the consent informed. Review of eligibility criteria.			
Research Assistant		VERIFICATION of FINDRISC, Randomization and data processing on the platform			
Research Assistant		Data processing on the platform to the corresponding group			
Laboratory		Implementation of POC-A1c			

CRS			Follow-up call 30 days after the PGT request.	Follow-up call - 30-90 days after admission to the study in patients not attending OGTT.	Verification call 30 days from the report of the result of the requested test. To those who present an impaired OGMP and have requested a control doctor.

Bias Control

- **Bias derived from the randomization process:** it is carried out through the Office - Excel platform by means of algorithms for the generation of random numbers and their assignment to the specific group, by means of a simple impaired randomization; in order to maintain the masking of the assignment, a number (1-2) will be assigned to classify the intervention and its comparator, keeping this hidden from most researchers.

- **Bias due to deviations from planned interventions:** from study design, with simple randomization, the subject who has received a group assignment cannot move on to the other.
- **Bias due to the lack of outcome data:** The number of stratified lost data of intervened versus non-intervened will be evaluated, if it exceeds 5% analysis and data imputation will be made.

- **Bias in outcome measurement:** the outcome of the OGTT sampling is sufficiently robust not to be affected by the research team, the participant itself or external factors.

- **Bias in the selection of the reported result:** at this point it is mentioned how the creation of surrogate outcomes not proposed in the protocol will be avoided and how consistency will be maintained in terms of the applicability of statistical terms, that is, only what is proposed in the data analysis will be carried out.

Statistical analysis plan

Description of statistical methods

For the primary objectives, the proportions of patients who attended the performance of the GTT in each of the groups will be obtained and the statistical significance test will be applied for superiority in the follow-up ratio of the intervention group (A) over the control group (B). Additionally, descriptive statistics will be obtained regarding the dynamics of application of the confirmatory test (i.e., latency time).

The variables will be checked for normality using the Kolmogorov-Smirnoff test. For quantitative variables, data shall be expressed as mean and standard deviation, or median and interquartile range 25%-75%, as the case may be.

For qualitative variables, proportions (%) will be determined. The continuous data between both groups will be analyzed with the T test if the distribution of the variables is normal or with the Mann-Whitney test if they are not. The analysis of the categorical data between two groups will be carried out with the chi-Square or Fisher test as appropriate.

An analysis will be carried out on the conditional probability of reaching a OGTT test: P(perform OGTT | FINDRISC >= 12)

P(perform OGTT | POC-A1c >=5.7% and FINDRISC >=12)

An analysis will be performed to identify risk factors for not performing the PGT, the dependent variable will be dichotomous. The main independent variable will be dichotomous corresponding to the control and intervention group. The control variables will be: age,

gender, type of affiliation, FINDRISC score and POC-A1c value (for those in which it is available) and others that are considered possible variables of confusion.

In order to analyze these associated factors, it is proposed to carry out a generalized linear model of binomial type or poison type with robust errors, in order to evaluate the influence of the factoris sociodemographic and with relevance / biological and contextual plausibility in the aforementioned outcome (non-realization of OGTT). The partnership measures will be presented through RR with their corresponding 95% confidence interval. A bivariate and multivariate analysis will be carried out to identify possible confusion or interaction for which the probability of performing the OGTT should be adjusted. Under the methodology proposed by Furnival-Wilson (1974) a reduced model will be estimated, using the logarithmic probabilities of the candidate models in order to establish the most parsimonious model. The goodness of fit of the models and the assumptions underlying the selected methodology will be evaluated. The statistical package where the analyses will be carried out is Stata 16MP.

Sample size

The study is designed to detect a 10% difference in going to the laboratory for OGPT between the intervention group (60%) and the control group (50%) considering a power of 80% and a confidence interval range of 95%.

Considering that some people with positive FINDRISC (i.e., greater than or equal to 12) will have a normal APOC-A1c, the number of participants in the intervention group (i.e., group A) will be increased by 30% to ensure sufficient subjects available for analysis with completely positive classification. This percentage corresponds to patients without glycemic alterations or DM2 identified in the FINDRISC validation study (9).

According to this and considering that the primary endpoint is a categorical variable, an initial sample of 784 randomized subjects (392 in each arm) was calculated, after the adjustments the sample is of 902 subjects distributed asymmetricallye (510 in group A or intervention and 392 in group B or control).

It is expected that the proportion of patients with FINDRISC greater than or equal to 12 will be 30% of the patients to whom the questionnaire is applied, according to this the expected total of Sieved patients is 3005. However, the total number of patients screened can be extended to complete the goal of randomized patients.

Level of significance

According to the described methodology, the significance level for the primary objective is 0.05.

Procedure to Explain Missing Data

Any deviation from the statistical plan will be discussed with all authors for approval.

Selection of subjects to be included in the analyses

The final analysis will include all individuals with complete data.

Ethical considerations

The research group will submit to the Ethics Committee for consideration all required documentation from the study, explain the risks and benefits and ask for their written consent. Each participant shall have the right to leave the study when he/she so arranges. The study will follow the Good Clinical Practice regulations of the Helsinki Declaration. An adverse effects data collection sheet will be used, it is estimated that possible adverse effects will be related to taking capillary puncture for POCA1C (puncture site infection and pain or dizziness/vomiting).

Data management and record keeping

Data management and record keeping will be carried out in accordance with the current procedures of MetricsMed and a specific parameterization is contemplated for the implementation of this project.

Financing and insurance (budget and schedule of activities)

See annex budget 5.

Publication Policy

The publications will be based on data from the center, analyzed according to the protocol. Researchers undertake not to publish data obtained in a centre or in a small group of centers before the main publication (or updates of the same), unless they are formally accepted by all other researchers. Authorship, order of authors, publications and results of the study shall be determined in accordance with the authors according to international standards for publications.

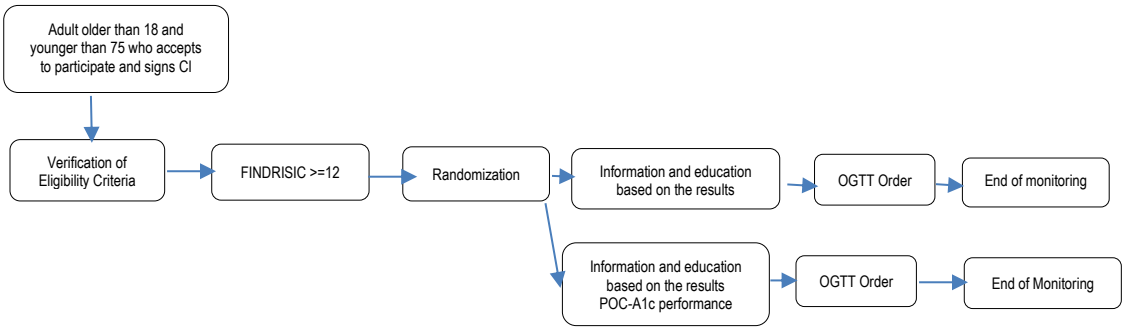
Annexes

1. Flow of interventions and procedures
2. Informed consent
3. FINDRISC Questionnaire
4. Table of variables
5. Schedule of activities – Budget

Annex 1: Flow of interventions and procedures

Annex 2: Informed consent

View attachment



Annex 3: FINDRISC Questionnaire

FINDRISIC QUESTIONNAIRE

1. Age
   - <45 years old ..... 0 points
   - 45-54 years old ..... 2 points
   - 55-64 years old ..... 3 points
   - >65 years old ..... 4 points
2. IMC (kg/m^2)
   - <25 ..... 0 points
   - 25-30 ..... 1 point
   - >30 ..... 3 points
3. Waist permitter

Men	Women
<94 cm	<80 cm .....0 points
94-102 cm	80-88 cm ..... 3 points
>102 cm	>88 cm ..... 4 points

4. Do they performs at least 30 minutes of physical activity at work on free time?
   - YES ..... 0 points
   - NO ..... 2 points
5. How often do they eat fruits or vegetables?
   - Every day ..... 0 points
   - Not every day ..... 1 points
6. Do they have high-blood pressure or take daily medication for hypertension?
   - NO ..... 0 points
   - YES ..... 2 points
7. Have they ever had high glucose levels?
   - NO ..... 0 points
   - YES ..... 5 points
8. Has any of their family members or relatives ever been diagnosed with diabetes?
   - NO ..... 0 points
   - YES... grandparents, uncles, aunts, cousins...3 points
   - YES ... parents, siblings, children ..... 5 points

Taken from ScienceDirect, Spanish clinical magazine, Volume 210, Issue 9, October 2010, pages 448-453

Annex 4: Table of variables.

Variable	Conceptual Definition	Operational Definition	Measurement scale
Demographics			
Identification	Citizenship Card Number	Integers	Discrete Quantitative Ratio
Health Coverage	Health care provider according to Colombian legislation, can be subsidized, contributory according to the social stratum of the person.	EPS –S (Subsidized) EPS –C (Contributory) Other (Exception Regime)	Qualitative Dichotomous
Gender	Sex of the patient	Male Female	Qualitative Nominal Dichotomous
Date of Birth	Main facts about the birth of a person according to the data issued in the official record or document.	Day Month Year	Quantitative Discrete
Marital Status	Permanent status of a natural (natural) person in relation to his or her personal circumstance and legislation.	Single Married Widower Divorced Free Union Separate	Qualitative Dichotomous Nominal
Last grade of schooling obtained	Degree of instruction by the school, parents, or caregiver.	Primary Secondary Technical Technology University Without studies	Qualitative Dichotomous Nominal
Employment Status	Set of activities that are carried out with the aim of reaching a goal, solving a problem or producing goods and services to meet human needs. Are you? Doing any paid (paid) work right now?	Yes No	Qualitative Dichotomous Nominal
Socio-economic stratum	Classification into strata of residential properties that must receive public services	1 2 3 4 5 6	Qualitative Ordinal
Anthropometric (non-invasive) measurements			
Weight	Magnitude in kilograms of a subject	Measured in kilograms (Kg)	Continuous Quantitative of Reason
Size	Height in centimeters of a subject	Measured in centimeters (Cm) with conversion to meters (mt)	Continuous Quantitative of Reason

Waist	Circumference measurement performed 1cm below the navel to determine abdominal obesity and expressed in centimeters.		Measured in centimeters (Cm)	Continuous Quantitative of Reason
BMI	Weight in kilograms divided over the size in meters squared		Measured in kg/m2	Continuous Quantitative of Reason
Family History				
Family member over 18 years of age with Diagnosis of DM	History of Diabetes Mellitus in direct family	Have any of your close relatives or other relatives been diagnosed with diabetes?	No Yes: grandparents, aunt, uncle , first cousin (not parents, siblings or children) Yes: parents or siblings	Nominal qualitative
Risk factors				
Diabetes Mellitus	Disease where there is excess blood sugar (glucose) from Pancreatic failure (Endocrine organ)	Has a doctor, nurse, or other health professional ever told you that you have or had Diabetes or high blood sugar?	Yes No	Dichotomous qualitative
Treatment for the Hipertension	Medicine that regulates the blood pressure	Do you take the medication for hypertension regularly?	Yes No	Dichotomous qualitative
Physical activity	Any body movement produced by skeletal muscles, with the consequent consumption of energy.	Usually perform at least 30 minutes of physical activity, at work and / or in free time?	Yes No	Dichotomous qualitative
Consumption of fruits and vegetables	Feeding from fruits and vegetables	How often do you eat vegetables or fruits?	Every day Not every day	Dichotomous qualitative
Biochemical Variables				
POC-A1c	Glycosylated Hemoglobin at Point of Care	PoC-A1c result	% or mmol/mol	Quantitative of Continuous Ratio

OGTT	Oral glucose tolerance test.	Result of the OGTT	mg / dl	Quantitative of Continuous Ratio
Date of Take OGTT	Date of performing the test	Date of OGTT Test	day/month/year	Discrete Quantitative
Risk calculation				

Screening result by FINDRISC	Scale to detect patients at higher risk of developing T2DM in the next ten years	Final result of FINDRISC	Points. Integer numeric value (discrete)	Quantitative Discrete
Final Diagnosis				
Patient presents Diabetes	Disease where there is excess blood sugar (glucose)from pancreatic failure (endocrine organ) as of performed diagnosis test.	Result according to OGTT or POC A1C and guidelines of clinical practice guidelines -, ADA	Ye s No	Qualitative Dichotomou s

Annex 5. Schedule of activities

- Schedule
  - Enlistment November 2021- January 2022
  - Start of Prescreening December 2021
  - Recruitment May - September 2022
  - Database review and debugging – February 2023
  - Information analysis - February 2023
  - Clinical study report –March 2023
  - Final report (article ready for publication) April-May 2023

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I, the undersigned, do hereby certify that I am fluent and competent in both, the English and Spanish languages, and that I have made the above translation from the original document in the Spanish language and the same is a true and complete translation to the best of my knowledge, ability, and belief. CAYETANO EDUARDO FORERO OROZCO, Sworn Translator and Interpreter Resolution # 502, – National University of Colombia – Bogotá, D.C. Place, and date of this translation: Bogotá, Colombia, 06-24-2022. Mobile telephone number: (57) 318 848 1431 Email: eduardoforeroo@gmail.com - Sworn Translation # 4917.

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