Lifestyle Intervention Clinical Trial for the Remission of Type 2 Diabetes Mellitus in Primary Care (CREDOenAP) [Ensayo clínico de intervención estilo de vida para la reversión de Diabetes Mellitus tipo 2 en Atención Primaria (CREDOenAP)]

Protocol Number*: <Number>

National Clinical Trial (NCT) Identified Number: <Number, once assigned by CT.gov>

Principal Investigator*: Alexandre Ternianov.

PhD, Specialist in Family and Community Medicine, Parc Sanitari Pere i Virgili. Primary and Community Care Research Group in Barcelona (APICBA), Hospital del Mar Research Institute.

Sponsor: Parc Sanitari Pere i Virgili

Funded by: Parc Sanitari Pere i Virgili

Version Number: Not applicable; this is the first version of the protocol

Date: 2025-09-04

Table of Contents

STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with the International Council on Harmonisation Good Clinical Practice (ICH GCP) guidelines, the Declaration of Helsinki, and applicable European Union and Spanish regulations governing clinical research with human participants, including:

- Regulation (EU) No 536/2014 on clinical trials on medicinal products for human use.
- Spanish Royal Decree 1090/2015, of 4 December, regulating clinical trials with medicinal products, Ethics Committees for Research with Medicinal Products (CEIm), and the Spanish Clinical Studies Registry (REec).

All investigators and clinical trial site staff responsible for the conduct, management, or oversight of the trial have completed training in Human Subjects Protection and ICH GCP. The study has been reviewed and approved by the Ethics Committee for Research with Medicines (CEIm) of Parc de Salut MAR, Barcelona, Spain. The Committee, both in its composition and in its Standard Operating Procedures (SOPs), complies with Good Clinical Practice (GCP) guidelines (CPMP/ICH/135/95).

The protocol, informed consent form(s), recruitment materials, and all participant materials will be submitted to the CEIm of Parc de Salut MAR for review and approval. Approval of both the protocol and the consent form(s) must be obtained before any participant is consented. Any amendment to the protocol will require review and approval by the CEIm of Parc de Salut MAR before the changes are implemented to the study. All changes to the consent form(s) will be CEIm of Parc de Salut MAR approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

INVESTIGATOR'S SIGNATURE

The signature below constitutes the approval of this protocol and provides the necessary assurances that this study will be conducted according to all stipulations of the protocol, including all statements regarding confidentiality, and according to local legal and regulatory requirements and applicable US federal regulations and ICH guidelines, as described in the *Statement of Compliance* above.

Principal Investigator or Clinical Site Investigator:

Signed: _____ Date: _____

Name*: Alexandre Ternianov

Title*: PhD, Specialist in Family and Community Medicine

Investigator Contact Information
Affiliation*: Primary and Community Care Research Group in Barcelona (APICBA), Hospital del Mar Research Institute, Parc Sanitari Pere Virgili, Barcelona, Spain.
Address: 30 Esteve Terradas Street, 08023 Barcelona, Spain
Telephone: +34 932 59 40 00
Email: *aternianov@perevirgili.cat*; *ncarrilero@perevirgili.cat*; averas@perevirgili.cat

1 SUMMARY OF THE PROTOCOL

1.1 SYNOPSIS

Title: Lifestyle Intervention Clinical Trial for the Remission of Type 2 Diabetes Mellitus in Primary Care (CREDOenAP) [Ensayo clínico de intervención estilo de vida para la reversión de Diabetes Mellitus tipo 2 en Atención Primaria (CREDOenAP)]

Grant Number: *N/A*

Study Description: Intervention program with intensive lifestyle counseling, added to standard pharmacological treatment subsequently adjusted according to clinical needs and outcomes. The intervention will last 6 months and consists of biweekly in-person and telephone visits. Patients will follow a personalized dietary plan with carbohydrate restriction, based on the recommendations of the American Diabetes Association; engage in moderate and accessible physical activity; implement circadian rhythm regularization; and receive psychological counseling and support.

Objectives*:

Primary objective:

To quantify the proportion of Type 2 Diabetes (T2DM) remission among participants without evidence of absolute insulinopenia enrolled in the lifestyle intervention program (CREDOenAP) at the end of the program (6 months).

Secondary objectives:

- To quantify the percentage of T2DM remission among participants in the lifestyle intervention program (CREDOenAP) one year after completion of the program (18 months).
- To determine the nutritional, physical activity, and quality-of-life patterns of participants in the CREDOenAP program before, at the end of the intervention and one year after (18 months).
- To assess anthropometric, metabolic, and imaging markers of cardiovascular risk in participants in the CREDOenAP program before, at the end of the intervention (6 months) and one year after completion (18 months).

Endpoints*:

Primary Endpoint:

- Percentage of participants achieving type 2 diabetes remission at 6 months, defined as HbA1c <6.5% after 6 months of intervention and at least 3 months without antidiabetic medication. HbA1c will be determined through fasting blood analysis (minimum 8 hours).
- Percentage of participants achieving T2DM remission at 6 months, defined as fasting venous plasma glucose <126 mg/dL after 6 months of intervention and at least 3 months without antidiabetic medication. Fasting glucose will be measured through venous blood analysis after a minimum 8-hour fast.

Secondary Endpoints:

- Percentage of participants maintaining type 2 diabetes remission at 18 months, defined as HbA1c <6.5% after 12 months post-intervention and at least 9 months without antidiabetic medication.

- Percentage of participants maintaining type 2 diabetes remission at 18 months, defined as fasting venous plasma glucose <126 mg/dL after 12 months post-intervention and at least 9 months without antidiabetic medication.

- Change in dietary patterns at 6 and 18 months, assessed using a validated 24-hour dietary recall questionnaire, to evaluate adherence to the nutritional component of the intervention.

- Change in physical activity level at 6 and 18 months, measured using the International Physical Activity Questionnaire (IPAQ).

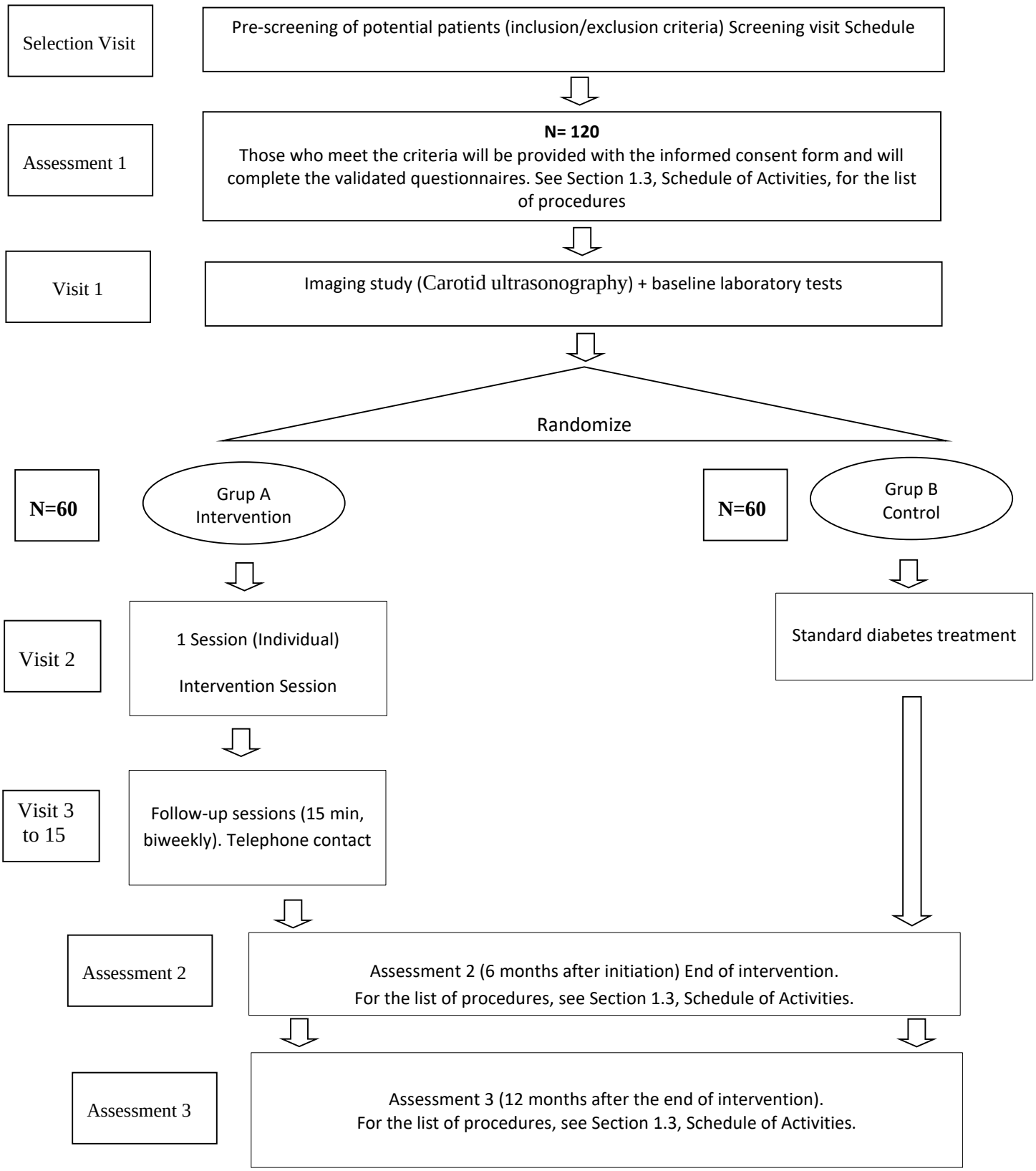
- Change in health-related quality of life at 6 and 18 months, assessed using validated instruments such as the SF-36 or EQ-5D questionnaires.

- Change in cardiovascular risk factors at 6 and 18 months, including blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, Apo B100, triglycerides, and presence and size of carotid atherosclerotic plaques.

- Change in metabolic indicators at 6 and 18 months, including weight, Body Mass Index (BMI), waist

	circumference, insulin resistance (HOMA-IR index), pancreatic beta-cell function (HOMA-B index), and fasting insulin.
Study Population:	The study population consists of patients with type 2 diabetes (T2DM) assigned to the Primary Care centers of Barceloneta and Larrard at Parc Sanitari Pere Virgili, Barcelona.
Phase* or Stage:	N/A.
Description of Sites/Facilities Enrolling Participants:	Multicenter Study Sites Barceloneta Primary Care Center, Parc Sanitari Pere Virgili, Barcelona, Spain Larrard Primary Care Center, Parc Sanitari Pere Virgili, Barcelona, Spain
Description of Study Intervention/Experimental Manipulation:	The program consists of biweekly in-person and telephone visits, focused on implementing a personalized dietary plan with carbohydrate restriction, based on the American Diabetes Association recommendations; moderate and accessible physical activity; circadian rhythm regularization; and psychological counseling and support.
Study Duration:	3 years.
Participant Duration:	18 months (6 months of intervention and follow-up assessments one year after completion of the intervention).

1.2 SCHEME


Selection Visit
Pre-screening of potential patients (inclusion/exclusion criteria) Screening visit Schedule
Assessment 1
N= 120
Those who meet the criteria will be provided with the informed consent form and will complete the validated questionnaires. See Section 1.3, Schedule of Activities, for the list of procedures
Visit 1
Imaging study (Carotid ultrasonography) + baseline laboratory tests
Randomize
N=60
Grup A
Intervention
N=60
Grup B
Control
Visit 2
1 Session (Individual)
Intervention Session
Standard diabetes treatment
Visit 3 to 15
Follow-up sessions (15 min, biweekly). Telephone contact
Assessment 2
Assessment 2 (6 months after initiation) End of intervention.
For the list of procedures, see Section 1.3, Schedule of Activities.
Assessment 3
Assessment 3 (12 months after the end of intervention).
For the list of procedures, see Section 1.3, Schedule of Activities.

1.3 SCHEDULE OF ACTIVITIES

	Screening / Selection	Assessment 1	Visit 1: Carotid ultrasonography + laboratory analyses	Randomization	Visit 2: Intervention session	Visits 3 to 15: Biweekly telephone contacts	Assessment 2 (6 months)	Assessment 3 (18 months)	End of study
Assessment of inclusion/exclusion criteria	X								
Signing of informed consent		X							
Collection of sociodemographic variables		X							
Review of medical history and current medication		X						X	
Anthropometric measurements (weight, height, BMI, waist circumference)		X					X	X	
Health-related quality of life questionnaire (SF-36)		X					X	X	
Dietary questionnaire (24-hour recall)		X				X	X	X	
Physical activity questionnaire (IPAQ)		X					X	X	
Laboratory analyses (HbA1c, glucose, insulin, lipids, etc.)			X				X	X	
Imaging studies (Carotid ultrasonography)			X				X	X	
Randomization				X					
Adverse event recording		X					X	X	X
Telephone follow-up for clinical status						X			

2 INTRODUCTION

2.1 STUDY RATIONALE

Type 2 diabetes (T2DM) represents a major public health problem, with its incidence rapidly increasing worldwide. In 2014, 8.5% of the global population was affected by this disease. (*Hambleton et al., 2013*). The results of *Di@bet.es* (*Soriguer et al., 2012*), the largest epidemiological study conducted in Spain revealed a prevalence of 13.8% for type 2 diabetes among adults over 18 years of age (5.3 million people), of whom 43% (2.3 million) were undiagnosed at the time of the study. Traditionally, type 2 diabetes (T2DM) has been considered a progressive and irreversible disease. This hypothesis was supported by a series of studies showing that 50% of individuals required insulin therapy 10 years after T2DM diagnosis, along with a progressive loss of insulin production. ("*Effect of Intensive Blood-Glucose Control with Metformin on Complications in Overweight Patients with Type 2 Diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group.," 1998; "U.K. Prospective Diabetes Study 16. Overview of 6 Years' Therapy of Type II Diabetes: A Progressive Disease. U.K. Prospective Diabetes Study Group.," 1995; Rudenski et al., 1988*). However, these hypotheses were based on studies with small sample sizes (*Rahier et al., 2008; Rudenski et al., 1988*) or on data from groups of individuals who gained weight steadily (approximately 5 kg in the intensively treated group *("Effect of Intensive Blood-Glucose Control with Metformin on Complications in Overweight Patients with Type 2 Diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group.," 1998; "U.K. Prospective Diabetes Study 16. Overview of 6 Years' Therapy of Type II Diabetes: A Progressive Disease. U.K. Prospective Diabetes Study Group.," 1995*). However, this paradigm has been shifting due to new evidence suggesting that intensive lifestyle interventions can achieve reversal or remission of the disease.

The objective of this study is to evaluate the effectiveness of the CREDOenAP program (Counseling for the Reversal of Diabetes in Primary Care), a multicomponent intervention based on intensive lifestyle modification, implemented in the primary care setting. The program focuses on four key pillars: a carbohydrate-restricted diet based on whole foods, daily physical activity, smoking and alcohol cessation, and psycho-emotional support (*Committee ADAPP, 2021*).

The intervention program is based on both WHO and ADA recommendations to address physical inactivity, diet, smoking, and alcohol consumption, as well as local dietary habits, prioritizing fresh, whole, locally sourced foods rather than processed, prepackaged, or substitute products. The program will utilize the usual resources of Family and Community Medicine, including standard in-person consultations and telehealth*("5. Facilitating Behavior Change and Well-Being to Improve Health Outcomes: Standards of Medical Care in Diabetes—2022," 2022; Committee ADAPP, 2021*).

It is expected that the changes induced by this intervention will result in improved glycemic control and, ultimately, partial or complete remission of type 2 diabetes (T2DM), defined according to the American Diabetes Association (ADA) consensus criteria as HbA1c <6.5% without pharmacological treatment for at least 3 months *("6. Glycemic Targets: Standards of Medical Care in Diabetes—2022," 2022*). In addition to potential T2DM remission, improvements in body

weight and cardiovascular risk profile are also anticipated, which may translate into reduced utilization of healthcare services and resources (*Committee ADAPP, 2021*).

It should also be noted that, to date, no methodology for T2DM reversal has been evaluated in patients under primary care follow-up in our setting and following a real-food diet. Developing such interventions and assessing their effectiveness is crucial for a systematic, multicomponent approach based on evidence-based medicine principles, adding value to routine primary care practice.

2.2 BACKGROUND

This study is based on the recommendations of the World Health Organization (WHO) and the American Diabetes Association (ADA). The intervention avoids the use of processed or dietary substitute products and promotes the consumption of fresh, locally sourced foods. It relies on the usual resources of Family and Community Medicine and can be implemented in primary care centers ("*5. Facilitating Behavior Change and Well-Being to Improve Health Outcomes: Standards of Medical Care in Diabetes—2022," 2022; Committee ADAPP, 2021*).

Low-Carbohydrate Diet

An available tool, in addition to oral and injectable antidiabetic medications such as insulin therapy and/or incretin receptor agonists, for reducing blood glucose levels, is a low-carbohydrate diet. (*Westman et al., 2006*). These diets are characterized by a reduced carbohydrate content, ranging from 5% to 45% of total daily intake, with a correspondingly higher proportion of dietary protein and fat, without restriction of total caloric intake. They can be an effective and safe tool for both weight management (*Harvey et al., 2019; Hession et al., 2009),* and glycemic control (*Sainsbury et al., 2018; Tay et al., 2015*). This has led to the inclusion of low-carbohydrate diets in the 2019 recommendations of the American Diabetes Association (ADA) (*ElSayed et al., 2022; Evert et al., 2019*).

Several additional beneficial effects of low-carbohydrate diets beyond weight and glycemic control have also been described: improvement of lipid profiles compared with high-carbohydrate diets (*Tay et al., 2015*), and also compared with low-fat diets (*Gjuladin-Hellon et al., 2019)*; reduction of cardiovascular risk (*Harvey et al., 2019; Hession et al., 2009)*; improvement of hepatic steatosis with very low-carbohydrate diets (*Dyńka et al., 2024; Jang et al., 2018),* as well as with low-carbohydrate Mediterranean diets (*Gepner et al., 2019*); improvement of epileptic conditions with very low-carbohydrate diets (*García-Peñas, 2016; Paoli et al., 2013)*; and beneficial effects for the prevention and adjuvant therapy of various cancers with very low-carbohydrate diets (*Weber et al., 2018*).

Diabetes Reversal – Non-Pharmacological Approaches

In the United Kingdom, within primary care settings, the DiRECT series of studies *(Lean et al., 2018*), were conducted, focusing on weight loss through a low-calorie diet. These studies were designed to evaluate whether effective weight control could induce sustained remission of type 2

diabetes (T2DM), restricting the participation to individuals aged 20–65 years who had been diagnosed with T2DM within the past 6 years, had a body-mass index of 27–45 kg/m², and were not receiving insulin. In the DiRECT study (149 participants per group), conducted across 49 primary care practices in Scotland and England, 24% of participants in the intervention group achieved a weight loss of 15 kg or more at 12 months, compared to none in the control group ($P < 0.0001$). T2DM remission was achieved in 46% of participants in the intervention group and 4% in the control group (odds ratio 19.7; 95% CI 7.8–49.8; $P < 0.0001$). A clear correlation was observed between remission rates and weight loss. The DiRECT program maintained remission at 24 months in more than one-third of participants with T2DM (*Lean et al., 2019*)with sustained remission associated with maintenance of the achieved weight loss.

This weight-loss-focused approach with dietary caloric restriction has been applied in other studies, achieving diabetes remission rates ranging from 47.2% (*Yang et al., 2023)* to over 60% of participants (*Taheri et al., 2020*), using various caloric restriction strategies and more restrictive inclusion criteria.

Another research group in the United Kingdom has published several articles in the form of clinical audits, reporting beneficial effects of diabetes remission through carbohydrate restriction. These effects include improvements in arterial hypertension, renal function, dyslipidemia, weight loss, and other metabolic parameters. (*Unwin et al., 2020, 2021, 2023; D. J. Unwin et al., 2019*).

In a series of publications, a telemedicine intervention group in the United States demonstrated several metabolic benefits of type 2 diabetes (T2DM) reversal through nutritional ketosis, with or without weight loss and without intentional caloric restriction. (*Athinarayanan et al., 2019; Bhanpuri et al., 2018; Hallberg et al., 2018; McKenzie et al., 2017*).

A consensus panel of ADA experts has developed and agreed upon criteria and definitions for the terms reversal, partial remission, complete remission, and prolonged remission of type 2 diabetes (T2DM) (Riddle et al., 2021). Diabetes remission is defined as achieving glycemic levels (fasting plasma glucose and HbA1c) below the minimum thresholds required for a T2DM diagnosis, i.e., fasting plasma glucose <126 mg/dL or HbA1c <6.5%.

To meet remission criteria, participants must be free from any pharmacological therapy or procedures (e.g., gastric band adjustments) for at least 3 months.

Lifestyle and Type 2 Diabetes

The WHO Global Action Plan for the prevention and control of chronic diseases, such as type 2 diabetes (T2DM), hypertension, obesity, and at least 13 obesity-related cancers *(CDC, 2017; Secretan et al., 2016*), recommends focusing efforts on addressing harmful lifestyle factors, including tobacco and alcohol use, physical inactivity, and unhealthy diet (*World Health Organization, 2013).*

According to the ADA, diabetes self-management education and support are essential to achieve therapeutic goals for type 2 diabetes (T2DM). These measures include medical nutrition therapy, physical activity, counseling for smoking cessation, and psychosocial support *(Committee ADAPP, 2021*).

Type 2 Diabetes – Current Management and Proposed Improvements

Although nutrition and physical activity are placed at the center of international guidelines for diabetes management (ADA/EASD), in clinical practice the pharmacological approach is clearly predominant. Economic data indicate that the cost of diabetes is increasing each year, with the largest share attributed to pharmaceutical expenditures. (*Crespo et al., 2015*). Currently, reversal and remission of type 2 diabetes (T2DM) are not considered primary treatment goals, with management focused on maintaining metabolic values within target ranges.

In the context of Spain, most interventions follow a pharmacological approach, representing high-cost measures for the healthcare system. The CREDOenAP intervention could provide evidence on lifestyle-focused strategies as a therapeutic pillar for T2DM remission, and evaluate their feasibility and effectiveness in primary care. Potential T2DM reversal through lifestyle intervention could have economic and organizational impact by reducing pharmaceutical costs and decreasing the number of medical visits associated with diabetes management.

2.3 RISK/BENEFIT ASSESSMENT

2.3.1 KNOWN POTENTIAL RISKS

Due to the nature of the study, which focuses on dietary and lifestyle changes in patients, the risks associated with this type of intervention are very low. However, potential risks may include:

- **Immediate risks:** Dietary changes and increased physical activity may trigger mild adverse effects. For example, participants may experience episodes of constipation, fatigue, or minor muscle discomfort related to increased physical activity.
- **Long-term risks:** In individuals with type 2 diabetes (T2DM) who discontinue pharmacological treatment due to metabolic improvement, there is a risk of hyperglycemia if the long term adherence to lifestyle programm fails. This risk will be minimized through close medical monitoring during the study.

No alternative interventions were proposed due to the low risk of adverse effects and to avoid interfering with the intervention as defined in the protocol.

2.3.2 KNOWN POTENTIAL BENEFITS

The expected benefits of this project, aimed at the remission of type 2 diabetes (T2DM) through lifestyle modification, include both immediate benefits for participants and long-term benefits with potential societal impact:

- **Immediate benefits:**
  - Improved glycemic control and avoidance of hypoglycemia
  - Weight loss
  - Reduction or discontinuation of antidiabetic medication
  - Improved overall well-being and mood
- **Long-term benefits:**
  - Possible sustained remission of T2DM
  - Improvement or reduction of cardiovascular risk and some types of cancer , (*Lakka et al., 2000; Nubiola et al., 2015; Rubins et al., 2002)*
  - Decreased healthcare and pharmaceutical burden, potentially resulting in cost savings for the healthcare system, including fewer specialist visits for diabetes complications, fewer primary care visits for diabetes monitoring, reduced medication costs, and lower expenses for injection and glucose monitoring supplies (pens, test strips, educational materials, etc.)
  - Improved patient quality of life, enabling simpler treatment with a positive impact on well-being and mood

2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

The intervention proposed in CREDOenAp involves a very low exposure to potential risks for patients. It is a non-invasive intervention that does not include the use of experimental drugs and is conducted under continuous clinical supervision and follow-up.

Moreover, CREDOenAP is justified by the potential clinical benefit to patients of achieving partial or total reversal (remission) of a chronic disease with high prevalence in the population.

Demonstrating the effectiveness of this intervention would provide crucial evidence for the healthcare system, enabling the implementation of cost-effective interventions in Primary Care.

3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
Primary		
To quantify the percentage of type 2 diabetes (T2DM) reversal among participants without signs of absolute insulinopenia enrolled in the CREDOenAP lifestyle intervention program at the end of the program (6 months).	Percentage of participants achieving type 2 diabetes (T2DM) remission at 6 months, defined as HbA1c <6.5% after 6 months of intervention and at least 3 months without antidiabetic medication. HbA1c will be measured from fasting venous blood samples (minimum 8 hours fasting). Percentage of participants achieving T2DM remission at 6 months, defined as fasting venous plasma glucose <126 mg/dL after 6 months of intervention and at least 3 months without antidiabetic medication. Fasting plasma glucose will be measured from venous blood samples after a minimum 8-hour fast.	These measures allow evaluation of the intervention's efficacy, as they are widely accepted indicators of type 2 diabetes (T2DM) remission. These criteria have been consensually established and accepted by international organizations such as the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).

Secondary		
1. To quantify the percentage of type 2 diabetes (T2DM) remission among participants in the CREDOenAP lifestyle intervention program one year after completing the program (18 months).	Percentage of participants maintaining type 2 diabetes (T2DM) remission at 18 months, defined as HbA1c <6.5% after 12 months following the intervention and at least 9 months without antidiabetic medication. Percentage of participants maintaining T2DM remission at 18 months, defined as fasting venous plasma glucose <126 mg/dL after 12 months following the intervention and at least 9 months without antidiabetic medication	These measures allow evaluation of the efficacy and long-term sustainability of the intervention, as they are widely accepted indicators of type 2 diabetes (T2DM) remission. These criteria have been consensually established and accepted by international organizations such as the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD).
2. To assess dietary patterns, physical activity, and health-related quality of life of participants in the CREDOenAP program at the end of the intervention and one year later.	Change in dietary patterns at 6 and 18 months, assessed using a validated 24-hour recall questionnaire, to evaluate adherence to the nutritional component of the intervention. Change in physical activity levels at 6 and 18 months, measured using the International Physical Activity Questionnaire (IPAQ). Change in health-related quality of life at 6 and 18 months, assessed using validated instruments such as the SF-36 or EQ-5D questionnaires.	Changes in the scores of the aforementioned questionnaires will allow evaluation of changes in dietary patterns, physical activity, and health-related quality of life.
3. To assess anthropometric, metabolic, and imaging markers for cardiovascular risk evaluation in participants of the CREDOenAP	Change in cardiovascular risk factors at 6 and 18 months, including blood pressure, total cholesterol, HDL cholesterol, LDL cholesterol, Apo B100, triglycerides, and the presence and	These measures will allow evaluation of key underlying mechanisms contributing to type 2 diabetes (T2DM) remission.

program at the end of the intervention (6 months) and one year later (18 months).	size of carotid atherosclerotic plaques. Change in metabolic indicators at 6 and 18 months, assessed through weight, body mass index (BMI), waist circumference, insulin resistance (HOMA-IR), pancreatic beta-cell function (HOMA-B), and fasting insulin levels.	
Tertiary/Exploratory		
To assess secondary metabolic markers for cardiovascular risk evaluation in participants of the CREDOenAP program at the end of the intervention (6 months) and one year later (18 months).	Change in metabolic indicators at 6 and 18 months, assessed through the diagnosis of Metabolic Syndrome, NAFLD Fatty Liver Index, and NAFLD Fibrosis Score.	These measures will allow evaluation of secondary underlying mechanisms for T2DM remission.
To assess healthy lifestyle habits and health-related quality of life patterns in participants of the CREDOenAP program at the end of the intervention and one year later.	Change in healthy lifestyle habits at 6 and 18 months, assessed through smoking habits (custom questionnaire), alcohol consumption (questionnaire and conversion calculator for standard drink units), and circadian habits (custom questionnaire). Change in quality of life at 6 and 18 months, assessed through medication use measured as Defined Daily Dose (DDD) of the active ingredient.	Changes in the scores of the aforementioned questionnaires and indicators will allow evaluation of changes in healthy lifestyle habits and quality of life.

4 STUDY DESIGN

4.1 OVERALL DESIGN

The study is designed as an open-label, randomized clinical trial. The strategy includes Group A – Intervention, which will undergo the CREDOenAP program, and a parallel control group, Group B – Control, which will receive standard T2DM care from a primary care team (family physicians

and nurses) without any intervention from the research team, except for data collection at baseline and at the end of each study phase.

The study has been designed to evaluate the effectiveness of a lifestyle-focused intervention (CREDOenAP) on T2DM reversal in primary care patients. It is a multicenter study involving two primary care centers in Barcelona (CAP Larrad and CAP Barceloneta).

The main hypothesis is that the proposed intervention, based on a structured and culturally adapted program, is effective in achieving biochemical and functional remission of T2DM. The study design corresponds to a randomized clinical trial aimed at establishing the initial efficacy of the intervention under real-world clinical practice conditions.

Each center will recruit participants who will be randomly assigned in a 1:1 ratio to each study arm. Recruitment is planned as follows:

- Center 1 (CAP Barceloneta): Group A – Intervention (20 participants) and Group B – Control (20 participants).
- Center 2 (CAP Larrard): Group A – Intervention (40 participants) and Group B – Control (40 participants).

Group A – Intervention, comprising a total of 60 participants (20 from Center 1 and 40 from Center 2), will receive standard care plus the CREDOenAP intervention.

Group B – Control, comprising a total of 60 participants (20 from Center 1 and 40 from Center 2), will receive standard care alone.

Both Group A – Intervention and Group B – Control will include patients meeting the inclusion and exclusion criteria, with assignment conducted via stratified randomization. Potential participants will be validated by a healthcare professional not involved in the intervention to exclude false positives due to registration errors.

For stratification, performed through statistical programming, relevant characteristics that may act as potential confounding variables will be considered. In this study, stratification will be based on:

- Healthcare center (Center 1: CAP Barceloneta / Center 2: CAP Larrard)
- Sex (Male / Female)
- Age (18–50 years / ≥50 years)
- Years since T2DM diagnosis (<5 years / ≥5 years)

The randomization sequence will be generated by an independent statistician.

The intervention has been designed to last 6 months. During this period, participants in the intervention group will receive individualized follow-up, both in-person and via telephone, aimed at achieving lifestyle changes (dietary modifications, increased physical activity, improved emotional management, etc.).

The control group will receive standard care for T2DM, with follow-up according to routine primary care practices. They will participate in periodic assessments but will not receive any components of the intervention program.

The study design includes a follow-up assessment 12 months after the end of the intervention (18 months from the start of the intervention) to evaluate the sustainability and long-term effects of the intervention.

Finally, no interim analyses or additional sub-studies are planned within this protocol.

4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

Evidence regarding the possibility of T2DM remission through patient-centered lifestyle interventions has generated increasing interest in replicating these results outside highly controlled settings. However, most available studies have been conducted in hospital or experimental environments, with resources that are difficult to implement or scale in primary care and at a large scale.

This protocol addresses this gap by focusing on the creation of an intervention adapted to primary care resources, where routine follow-up of T2DM patients is performed. This intervention will allow evaluation of both the effectiveness and feasibility of a program under real-world clinical practice conditions and which is using sustainable real food nutrition recommendations. Additionally, the use of a control group receiving standard care will facilitate comparison with currently available care, without introducing biases associated with placebo or other external factors.

The chosen intervention design—a block-randomized study stratified by key variables (center, age, sex, duration of diagnosis)—aims to ensure comparability between groups and minimize potential biases. The study is open-label, as blinding of participants and investigators is not feasible due to the behavioral nature of the intervention. (*Friedman et al., 2015*)

4.3 JUSTIFICATION FOR INTERVENTION

The intervention has been specifically designed for implementation in the primary care setting in Spain, based on the available scientific evidence on effective interventions for T2DM remission. This program combines individual sessions, biweekly telephone follow-up, and individualized clinical support.

The 6-month duration is based on previous studies demonstrating that this period is sufficient to achieve significant metabolic remission in patients with T2DM without insulinopenia. Biweekly follow-up aims to reinforce adherence, identify incidents, provide guidance and support, and monitor participants' health status.

A participant is considered sufficiently exposed to the intervention when at least 70% of the program has been completed. A minimum of 70% adherence to scheduled sessions and activities has been established in several studies as a reasonable threshold to ensure the effectiveness of lifestyle interventions. Completing at least 70% of the program allows participants to achieve significant clinical benefits, as reflected in systematic reviews on physical activity and dietary interventions. (*Burke et al., 2011; Zabaleta-Del-Olmo et al., n.d.)*

Furthermore, the World Health Organization highlights the importance of maintaining high adherence levels in long-term therapies to ensure optimal clinical outcomes (*WHO, 2003*). Therefore, in this study, participants who complete at least 70% of the planned intervention will be considered adherent, as this threshold is supported by scientific evidence to be sufficient for producing meaningful clinical changes.

4.4 END-OF-STUDY DEFINITION

For study completion, all participants must have attended all follow-up visits, with the final visit occurring 18 months after the start of the intervention. A participant will be considered to have completed the intervention if they have undergone the initial assessments, attended at least four biweekly telephone follow-up sessions, and completed the assessments at 6 months and 18 months from the start of the intervention. These stages are detailed in Section 1.3 (Activity Schedule).

5 STUDY POPULATION

The study population comprises adults over 18 years of age diagnosed with T2DM, without signs of insulinopenia. These individuals must be assigned to one of the primary care centers, CAP Barceloneta or CAP Larrad, which belong to the Catalan public health system in the city of Barcelona.

In 2024, according to the latest updated data, CAP Barceloneta had an assigned population of 15,426 individuals and CAP Larrad had 38,819 individuals. Of the total 54,245 people served across these two primary care areas, approximately 2,800 individuals (5.3% of the population) have an active diagnosis of T2DM. By sex, the estimated prevalence of T2DM is 6.0% in men and 4.6% in women.

The population selected for this study represents a clinical group characterized by overweight or obesity and poor glycemic control. However, one of the most relevant exclusion criteria is the absence of indications of potential insulin dependence. These characteristics are expected to form a sample representative of individuals with T2DM associated predominantly with obesity. This population group represents the patients most likely to benefit from the intervention.

Patient recruitment will be conducted through screening using health records, based on the inclusion and exclusion criteria detailed in this study. Compliance with these criteria will be evaluated by a physician external to the research team.

5.1 INCLUSION CRITERIA

The inclusion criteria for patient recruitment in this study are as follows:

1. Signed informed consent.
2. Men and women aged 18–80 years, inclusive.
3. Confirmed diagnosis of T2DM according to recognized diagnostic criteria (*Association, 2021)*
4. Most recent recorded hemoglobin A1c (HbA1c) > 6.5%.
5. Body Mass Index (BMI) greater than 27 kg/m².

Individuals considered eligible for recruitment must meet all of the above inclusion criteria and be able to comply with the activities described in the intervention process.

5.2 EXCLUSION CRITERIA

The exclusion criteria for this study are as follows (meeting any of these criteria precludes participation):

1. Failure to meet the diagnostic criteria for T2DM in the screening laboratory tests.
2. Being dependent for basic activities of daily living (Barthel score ≤ 90 points).
3. Lack of willingness to cooperate with the follow-up of the lifestyle intervention plan.
4. Presence of serious or terminal comorbidities significantly worsening short- to medium-term prognosis (active cancer, terminal chronic diseases, myocardial infarction within the last 6 months, acute heart failure or NYHA stage ≥ III, etc.).
5. History of ketoacidosis.
6. Presence of criteria or potential autoimmune insulinopenia (abnormal C-peptide, anti-GAD+ antibodies, pattern of basal and/or glucose-stimulated hypoinsulinemia).
7. Cognitive impairment.
8. Weight loss exceeding 5 kg in the past 6 months.
9. Significant changes in physical activity and/or dietary patterns in the past 6 months.
10. History of eating disorders.
11. History of substance abuse.
12. History of severe psychiatric disorders.
13. Pregnancy or intention to become pregnant within the study period.

5.3 LIFESTYLE CONSIDERATIONS

Since this study involves a behavioral intervention aimed at changing patients' lifestyle, participants must commit to following the recommendations upon which the intervention protocol is based. The restrictions and recommendations (detailed in Appendix 1) are as follows:

- Adherence to a low-carbohydrate Mediterranean diet. Participants should reduce or avoid the following:

  - Processed and ultra-processed foods
  - Added sugars and sweeteners (e.g., sugar, honey, syrups)
  - Starchy foods (e.g., bread, pasta, rice, potatoes, legumes, cereals)
  - High-fructose fruits (e.g., bananas, grapes, dates, tropical fruits)
  - Fruit juices and sugar-sweetened beverages (including "zero-calorie" drinks)
  - Fried foods (frying is discouraged; the only recommended oil is extra virgin olive oil, consumed raw)
- Avoid alcohol consumption
- Avoid tobacco use
- Daily physical activity:
  - Recommended 10,000 steps per day
  - Strength training (progressive and individualized): During the first two weeks, at least one hour of walking per day is recommended. Strength exercises will then be gradually introduced (e.g., two sets of 5–10 squats). Weightlifting routines may be added according to individual tolerance.
- Healthy circadian habits:
  - Maintain regular sleep schedules
  - Wake up between 6:00 and 8:00 a.m.
  - Sun exposure for 15 minutes (preferably between 7:00 and 9:00 a.m.)
  - Go to bed before 11:00 p.m.
  - Sleep approximately 8–9 hours per night
- No use of pharmacological treatments or supplements for weight or appetite control is allowed during the study.

5.4 SCREEN FAILURES

Screen failures are defined as participants who consent to participate in this study but are subsequently not assigned to the intervention or included in the study.

Participants who do not meet the eligibility criteria will continue to receive standard healthcare from their primary care team. Failure to participate in this study will not affect the patient's usual treatment or follow-up in any way.

This protocol does not include provisions for re-screening participants if their circumstances change and they subsequently meet the eligibility criteria.

5.5 STRATEGIES FOR RECRUITMENT AND RETENTION

The recruitment strategy includes:

1. Initial identification from patients' medical records to search for potential participants who meet the inclusion criteria.
2. Manual clinical confirmation by a physician external to the project, using the Shared Clinical History, to verify that selected candidates do not meet any exclusion criteria.

3. Contact with potential participants via telephone call, followed by an in-person visit to obtain signed informed consent.

Participation in the intervention is voluntary, and no material or financial incentives are provided.

No specific patient retention plan is included. Follow-up visits will be conducted as scheduled in the protocol. Appointment reminders will be provided, and during the visits, participants will receive positive reinforcement regarding the benefits of the intervention and their participation.

This protocol does not specifically include vulnerable populations. However, if during the course of the study a participant becomes part of a vulnerable group, their continued participation will be evaluated, prioritizing the participant's health and safety.

6 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S)

6.1 STUDY INTERVENTION(S) OR EXPERIMENTAL MANIPULATION(S) ADMINISTRATION

6.1.1 STUDY INTERVENTION OR EXPERIMENTAL MANIPULATION DESCRIPTION

This protocol describes an intervention focused on lifestyle changes, with the primary objective of achieving remission of T2DM. This goal is intended to be accomplished through modifications in patients' lifestyle factors, such as dietary patterns and regular physical activity.

Remission is considered achieved when HbA1c is < 6.5% for at least 6 months, including a minimum of 3 months without antidiabetic pharmacological treatment.

The control group will receive standard care for T2DM in the primary care setting.

6.1.2 ADMINISTRATION AND/OR DOSING

The intervention program will be conducted over a period of 6 months, with a final follow-up 12 months after the end of the intervention. Participants assigned to the intervention group will receive:

- Low-carbohydrate dietary plan, adapted to the Mediterranean diet.
- Promotion of physical activity, including light and progressive strength exercise plans.
- Dietary monitoring and logging.
- Follow-up of progress and relevant parameters measured during the intervention.

The intervention will be delivered by a family physician and the evaluations of the adherence to the programm will be monitored by the intervention team, consisting of a phamily physician, nurce and nutritionist. Sessions will take place at the primary care centers (CAP Barceloneta and CAP Larrard).

6.2 FIDELITY

6.2.1 INTERVENTIONIST TRAINING AND TRACKING

This protocol includes internal training for the intervention staff to ensure proper implementation of the program and fidelity to the outlined activities. Training will be provided prior to the start of the intervention and will include:

- Education on low-carbohydrate diets and their clinical application.
- Protocols and guidelines for conducting the intervention sessions.
- Procedures for maintaining intervention records.
- Training on the procedures for aortic imaging tests.

Any changes to the procedures described above will be officially documented and agreed upon with the intervention team.

6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

The process of randomization and group assignment will be carried out through a randomization system with a 1:1 allocation ratio. However, due to the nature of the present study, no blinding of participants or professionals is planned, as this is a behavioral intervention and blinding would be counterproductive to the development of the research.

On the other hand, in order to minimize potential biases:

- An external analysis will be conducted by professionals who are not involved in the screening or in the implementation of the intervention activities.
- Patient screening and randomization will be performed by a team of professionals independent from the intervention group.

6.4 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION ADHERENCE

To monitor and promote participant adherence to the intervention activities, biweekly telephone contacts will be conducted. During these contacts, the following will be performed:

- 24-hour dietary recall survey: using photographs of the participant’s food intake over one day, their diet will be recorded.
- Overall health check of the participant.
- Review and adjustment of daily exercise plan.

A participant will be considered adherent to the intervention if they complete the initial session and at least 70% of the follow-up sessions. All adherence information will be recorded in the official intervention log.

6.5 CONCOMITANT THERAPY

During the study, participants will be allowed to continue their usual treatment for concomitant conditions. However, the use or initiation of weight-loss medications (such as GLP-1 receptor agonists) or diets other than those specified in this protocol will be prohibited, as this constitutes an exclusion criterion for the intervention. Use of concomitant medications will be recorded at each study visit.

6.5.1 RESCUE THERAPY

In the event of a significant glycemic decompensation in any participant (HbA1c > 9% or presence of symptoms), the study team may initiate pharmacological treatment based on clinical judgment or refer the participant to their usual physician for further evaluation. The date, type, and dose of any medication initiated will be recorded.

7 STUDY INTERVENTION/EXPERIMENTAL MANIPULATION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

7.1 DISCONTINUATION OF STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

Participation in the study is voluntary, and participants may withdraw from the intervention at any time. Additionally, the study team may decide to discontinue a participant's involvement if any of the following conditions occur:

- Non-compliance with the intervention activities.
- Emergence of new comorbidities incompatible with the intervention.
- Deterioration of health status since the start of the intervention (e.g., significant involuntary weight loss).
- Experiencing discomfort related to the intervention, whether physical or psychological.

In the event of intervention discontinuation, the following information will be recorded:

- Date of discontinuation.
- Reason for discontinuation.
- Health status at the time of discontinuation.
- Plan to continue with the scheduled follow-up visits, provided the participant consents.

7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY

Any participant may permanently withdraw from the intervention at any time without providing justification and without affecting their routine medical care. Additionally, the study team may permanently discontinue a participant's involvement in the intervention if any of the following occur:

- Loss of any contact with the participant (see Section 7.3).
- Occurrence of significant medical changes (e.g., hospitalization, new pathologies incompatible with the intervention).
- Identification of exclusion criteria that were not previously detected.
- Pregnancy or explicit intention to become pregnant.
- Initiation of therapies incompatible with the intervention.
- Evidence that the participant no longer wishes to continue the intervention activities.

Replacement of participants may be considered only if the individual was assigned to the intervention group but did not start the activities. Participants who begin the intervention and subsequently cannot continue will not be replaced.

7.3 LOST TO FOLLOW-UP

A participant will be considered lost to follow-up if they fail to attend scheduled visits and cannot be contacted after three attempts (via telephone at different times of day).

To minimize loss to follow-up, the following measures will be implemented:

- Sending reminders prior to each scheduled visit.
- Rescheduling missed visits.
- Recording all contact attempts.

If these measures are unsuccessful and contact with the participant cannot be established, the participant will be classified as "lost to follow-up" and will be excluded from the intervention.

8 STUDY ASSESSMENTS AND PROCEDURES

8.1 ENDPOINT AND OTHER NON-SAFETY ASSESSMENTS

To evaluate the effectiveness of the CREDOenAP intervention on the different health indicators defined in the objectives, various variables will be collected.

Sociodemographic Variables

- **Sex:** dichotomous variable according to biological sex (Male/Female).

- **Age:** age at study entry.
- **Living situation:** current living arrangement (Lives alone / Lives with others).
- **Socioeconomic level:** determined using the individual health insurance card (TSI) based on the pharmaceutical copayment level. Copayment is calculated according to each individual's income and employment status. Based on the copayment contribution, individuals are categorized into four socioeconomic levels:
    - **Very low:** TSI 001, exempt from copayment. Includes individuals receiving minimum insertion income, active insertion income, guaranteed citizen income, exhausted unemployment benefits, or non-contributory pensions.
    - **Low:** TSI 002 (10% copayment) and TSI 003 (40% copayment). Population with annual income < €18,000.
    - **Medium:** TSI 004 (50% copayment) and TSI 006. Population with annual income €18,000–€100,000 or individuals in administrative mutual schemes.
    - **High:** TSI 005 (60% copayment). Population with annual income > €100,000.

Clinical Variables

- **Year of T2DM diagnosis:** year of T2DM registration in eCAP.
- **Main comorbidities:** the primary active diagnoses recorded in eCAP will be obtained and corroborated with the participant.

Primary Outcome Variables

All primary outcome variables will be measured, calculated, and recorded at study baseline, at the end of the intervention, and 12 months after the intervention.

- **Presence of T2DM remission** (according to ADA consensus definition, (*Riddle et al., 2021)***)**:
    - **Glycated hemoglobin (HbA1c):** T2DM remission will be considered if HbA1c is < 6.5% after 6 months of intervention and at least 3 months without antidiabetic medication. HbA1c will be determined by blood analysis after a minimum of 8 hours of fasting (*Association, 2021*)
    - **Fasting plasma glucose:** T2DM remission will be considered if fasting venous plasma glucose is < 126 mg/dL after 6 months of intervention and at least 3 months without antidiabetic medication. Fasting plasma glucose will be measured by venous blood analysis after a minimum of 8 hours of fasting (*Association, 2021*)

Secondary Outcome Variables

All secondary outcome variables will be measured, calculated, and recorded at study baseline, at the end of the intervention, and 12 months after the intervention.

a) Cardiovascular Risk Factors

- **Blood pressure:** Blood pressure will be measured three times after the participant has been seated at rest for 10 minutes with uncrossed legs. The mean of the last two measurements will be used for statistical analysis. Systolic and diastolic blood pressure will be reported in mmHg using a brachial cuff sphygmomanometer.
- **Total cholesterol:** Measured in mg/dL via blood analysis.
- **HDL cholesterol:** High-density lipoprotein (HDL) cholesterol measured in mg/dL via blood analysis.
- **LDL cholesterol:** Low-density lipoprotein (LDL) cholesterol measured in mg/dL via blood analysis.
- **Apolipoprotein B100 (ApoB100):** A protein involved in cholesterol transport and relevant for evaluating elevated cholesterol causes, measured in mg/dL via blood analysis.
- **Triglycerides:** Measured in mg/dL via blood analysis.
- **Presence and size of atherosclerotic plaques in carotid arteries:** Assessed via Carotid ultrasonography. If plaques are present, the total plaque area will be measured in cm^2, and changes in plaque area will be tracked throughout the study.

b) Metabolic Indicators

- **Weight:** Measured in kilograms using a calibrated scale.
- **Body Mass Index (BMI):** Calculated from weight and height using the formula: BMI = weight (kg) / [height (m)]².
- **Abdominal circumference:** Measured at the midpoint between the lowest rib and the iliac crest during maximal inspiration and expiration, in centimeters.
- **Insulin resistance:** Evaluated using the HOMA-IR index (Homeostasis Model Assessment of Insulin Resistance), which estimates insulin resistance and beta-cell function. Determined via blood analysis after a minimum 8-hour fast. Values above 2.5 may indicate T2DM. Calculated as: [fasting insulin (μU/mL) x glucemia basal (mmol/L)] / 22.5 = [fasting insulin (μU/mL) x (Glucemia basal (mg/dL) x 0,0555)] / 22.5 *(HOMA Calculator — Radcliffe Department of Medicine, n.d.*)
- **Pancreatic activity:** Assessed using the HOMA-B index, which evaluates the function and activity of pancreatic beta cells. HOMA-B, together with HOMA-IR, helps in the diagnosis of T2DM. Values between 167 and 175 are considered normal and not indicative of T2DM. Values below this range suggest impaired beta-cell function, resulting in insufficient insulin production (insulinopenia). *(HOMA Calculator — Radcliffe Department of Medicine, n.d.*)
- **Fasting insulin:** Measures the amount of insulin in a blood sample. Insulin is a hormone produced by the pancreas. Normal values range between 5–25 U/mL. It will be measured via blood analysis after a minimum 8-hour fast.
- **Metabolic Syndrome Diagnosis:** Refers to a cluster of metabolic abnormalities considered a high-risk factor for cardiovascular disease and other health complications. It will be assessed according to the criteria of the International Diabetes Federation (IDF) new classification.(*International Diabetis federation (IDF), 2006*) y National Cholesterol Education Program's Adult Treatment Panel III (NCEP ATP III)(*Alexander et al., 2003*).

Metabolic Syndrome Diagnosis is established if at least three of the following five criteria are present:

- Abdominal circumference: Men of European descent > 94 cm; Women of European descent > 80 cm. For other ethnicities, cut-off points are defined according to the International Diabetes Federation (IDF). (*López De La Torre et al., 2010)*
- Fasting glucose: > 100 mg/dL or receiving pharmacological treatment for hyperglycemia.
- Triglycerides: > 150 mg/dL or receiving lipid-lowering therapy.
- HDL cholesterol: < 40 mg/dL in men; < 50 mg/dL in women, or receiving lipid-lowering therapy.
- Blood pressure: Systolic > 130 mmHg or Diastolic > 85 mmHg, or receiving antihypertensive treatment.

- **NAFLD Liver Fat Score:** Non-alcoholic fatty liver disease (NAFLD) is a condition characterized by excessive fat accumulation in the liver. Its severity can vary according to the score: < –1.455 low risk, –1.455 to 0.675 intermediate risk, > 0.675 high risk (*Angulo et al., 2007; Kotronen et al., 2009*).

  The calculation is determined using the following formula:

  –2.89 + 1.18 × Metabolic Syndrome (Yes = 1 / No = 0) + 0.45 × T2DM (Yes = 2 / No = 0) + 0.15 × Fasting Insulin (mU/L) + 0.04 × Fasting Serum AST (U/L) – 0.94 × AST/ALT ratio

- **NAFLD Fibrosis Score:** The identification and quantification of fibrosis are clinically relevant since fibrosis is associated with an unfavorable clinical prognosis. An NFS > 0.676 indicates the presence of advanced fibrosis (*Angulo et al., 2007; Kotronen et al., 2009*). The calculation is determined using the following formula:

  –1.675 + 0.037 × Age (years) + 0.094 × BMI (kg/m²) + 1.13 × IFG/diabetes (Yes = 1 / No = 0) + 0.99 × AST/ALT ratio – 0.013 × Platelets (×10⁹/L) – 0.66 × Albumin (g/dL)

c) Healthy lifestyle habits

- **Physical activity:** Physical activity will be assessed using the International Physical Activity Questionnaire (IPAQ). It consists of seven questions regarding the frequency, duration, and intensity of physical activity (moderate and vigorous) performed during the previous seven days, as well as walking and sitting time on a typical workday. The questionnaire may be administered through face-to-face interview, telephone interview, or self-administered survey (*Mantilla Toloza & Gómez-Conesa, 2007*).
- **Nutritional and energy composition:** The *24-hour dietary recall questionnaire* will be administered at each biweekly visit. This questionnaire is a reference tool in most

nutritional studies (*Block, 1982; Fanelli & Stevenhagen, 1986; Gersovitz et al., 1978; Madden et al., 1976*), and will be used to determine the daily intake of each type of food (*Freedman et al., 2017*).

- **Smoking habits:** Using a study-specific questionnaire, participants will be directly asked: *Do you smoke?* (Yes/No). If the response is affirmative, participants will be asked: *How many cigarettes do you smoke per day?*
- **Alcohol consumption:** Alcohol intake will be quantified using a questionnaire combined with a standardized alcohol unit conversion calculator. Participants will be asked about their consumption of different alcoholic beverages during the previous seven days. Using the conversion calculator, the total alcohol content (in ml of pure alcohol) will be estimated to obtain the average daily alcohol intake (*Cálculo: Cuantificación Del Consumo de Alcohol - Fisterra, n.d.; Valencia-Martín et al., 2014*).
- **Circadian habits:** Using a study-specific questionnaire, participants will be directly asked: *What time did you go to bed yesterday?* and *How many hours did you sleep today?*

d) Quality of life

- **SF-36:** This is a generic scale that provides a health status profile and is applicable both to patients and to the general population. The 36 items of the instrument cover the following domains: Physical Functioning, Role Physical, Bodily Pain, General Health, Vitality, Social Functioning, Role Emotional, and Mental Health. For each domain, items are coded, aggregated, and transformed into a scale ranging from 0 (worst health status for that dimension) to 100 (best health status) (*Alonso et al., 1995*).

e) Medication consumption

- **Defined Daily Dose (DDD) by active substance:** DDDs of the active substances consumed will be classified according to ATC7. Each ATC classification has a defined daily dose based on international standards, which determine the recommended maximum daily amount for the approved indication of the active substance (*WHOCC, n.d.*).

Control variables and management of T2DM

Patients will be assessed during each follow-up telephone visit throughout the intervention, at the end of the intervention, and one year after its completion. For the control group (Group B), episodes will be identified through records in the electronic health record system (eCAP).

- **Number of hypoglycemia episodes**: Episodes of hypoglycemia detected by patients through capillary blood glucose levels and/or recorded in eCAP during the intervention (plasma glucose <60 mg/dl).
- **Number of symptomatic hyperglycemia episodes**: Episodes of hyperglycemia recorded in eCAP during the intervention (plasma glucose >350 mg/dl accompanied by compatible symptoms such as general malaise, nausea, asthenia, among others).

- **Total number of healthcare visits:** Annual contacts with the healthcare system including Primary Care (physicians and nursing), Specialized Care, and Emergency Care.
- **Number of diabetes-related emergency episodes:** Emergency visits related to diabetes during the intervention period.

Recruitment

Through the internal registry of the Primary Care Clinical Station (eCAP), patients with a diagnosis of Type 2 Diabetes Mellitus (T2DM) from each primary care center (CAP) will be identified. Potential participants will be validated by a physician not involved in the intervention, in order to exclude false positives due to registry errors and to confirm inclusion and exclusion criteria.

Randomization will be performed by stratifying according to the characteristics defined in section 6.2. Study Design.

Potential participants will receive an invitation to take part in the study during their last medical consultation (in person or by telephone) by their physician, nurse, or the principal investigator. They will then be scheduled for a screening visit with a member of the research team, following completion of the screening blood test. Patients will be informed of the necessary requirements for the laboratory tests (fasting status and first morning urine sample) as well as the location where they will be carried out (extraction and laboratory areas of each primary care center).

Screening and Study Inclusion Visit

During this visit, eligibility criteria will be assessed to determine whether patients meet the study selection requirements. Participants who fulfill the criteria will receive a detailed explanation of the study objectives and the implications of participation. They will be provided with the study information sheet and, if they agree to participate, will sign an informed consent form for data collection throughout the study. If consent is obtained, a physical examination (anthropometric measurements) will be performed, sociodemographic variables will be recorded, and participants will complete the questionnaires assessing quality of life, physical activity, nutritional status, and lifestyle habits (including substance use). Additionally, appointments will be scheduled for all participants to undergo the imaging test (Carotid ultrasonography).

Laboratory Tests

Blood and urine analyses will be performed at three different time points during the study: at baseline, at the end of the intervention, and 12 months after completion of the intervention. These analyses do not involve any additional procedures, as they are part of the routine clinical practice for monitoring and follow-up of all patients with type 2 diabetes mellitus (T2DM) in primary care. No requests, extractions, or analyses will be conducted outside of standard clinical care. The laboratory tests will include: Complete blood count, HbA1c, Creatinine, Glomerular filtration rate, GOT (AST), GPT (ALT), GGT, Ionogram, Lipid profile (Total cholesterol, HDL, LDL,

Triglycerides, Apo B100), Fasting insulin, Anti-GAD antibodies (only at baseline), Urine: sediment and albumin/creatinine ratio.

Imaging Diagnosis: Carotid ultrasonography

As part of the cardiovascular risk factor assessment, three ultrasound examinations of the carotides will be performed during the study: at baseline, at the end of the intervention, and 12 months after the completion of the intervention.

	1st Examination and Sample Collection T0 (Baseline / Start of Intervention)	**Follow-up Visits**	**2nd Examination and Sample Collection** T-6 months (End of Intervention)	**3rd Examination and Sample Collection T-18 months** (12 months after End of Intervention)
Questionnaires and Assessment Scales				
24-Hour Recall	x	x	x	x
SF36	x		x	x
IPAQ	x		x	x
Tobacco consumption	x	x	x	x
Alcohol consumption	x	x	x	x
Circadian cycle	X	X	X	x
Physical Examination (Anthropometric Measurements)				
Weight	x	x	x	x
Height	x			
Abdominal circumference	x	x	x	x
Blood Analysis				
Complete blood count$^{\alpha}$ (CBC$^{\alpha}$)	x		x	x
C-Reactive protein$^{\alpha}$ (CRP$^{\alpha}$)	X		X	X
HbA1c	X		X	X
Creatinine$^{\alpha}$	X		X	X
Glomerular filtration rate$^{\alpha}$ (GFR$^{\alpha}$)	X		X	X
Aspartate Aminotransferase (AST)	X		X	X

Alanine Aminotransferase (ALT)	X		X	X
Gamma-Glutamyl Transferase (GGT)	X		X	X
Alkaline Phosphatase[α] (ALP [α])	X		X	X
Amylase [α]	X		X	X
Total Blood Protein [α]	X		X	X
Electrolyte Panel [α]	X		X	X
Calcium [α]	X		X	X
Phosphate [α]	X		X	X
Lipid Profile (Total Cholesterol, HDL, LDL, Triglycerides, Apo B100)	X		X	X
Basal C-Peptide [α]	X		X	X
Anti-GAD Antibodies (GAD Ab)	X			
TSH[α]	X		X	X
Free T4 [α] (Free Thyroxine [α])	X		X	X
CA 19.9. [α]	X		X	X
Urine Analysis				
Urine Sediment [α]	X		X	X
Albumin/Creatinine Ratio [α]	X		X	X
Imaging Test (Ultrasound)				
Carotid ultrasonography	X		X	X
Type 2 Diabetes Management and Monitoring				
Hypoglycemia episode(s)		X	x	
Hyperglycemia episode(s)		X	x	

[α] Parameters to assess the participant's general health status. These parameters are included in the routine monitoring of a person with type 2 diabetes (T2DM).

[β] Only in cases of a discordant relationship between HbA1c values and plasma glucose.

Examinations, laboratory tests, imaging studies, and questionnaires will be conducted at the patient's primary care center (CAP Barceloneta or CAP Larrard) by healthcare personnel (physician/nurse according to the test and training) during regular working hours. Blinding will be implemented for the evaluators, as all tests and questionnaires will be carried out by personnel not

involved in the research team and not responsible for delivering the intervention, with no knowledge of the participant's assignment to group A or B in the study.

8.2 SAFETY ASSESSMENTS

The CREDOenAP program intervention is considered a low-risk intervention due to its behavioral nature. It does not involve the use of any drugs or invasive procedures. However, several measures have been planned to assess and ensure the safety of participants in the intervention:

- Adverse event monitoring: During the scheduled follow-up sessions within the intervention, the professional responsible for conducting the sessions will also be in charge of identifying and reporting any adverse events. Any signs of physical or emotional discomfort or change will be recorded. Subsequently, the event will be evaluated to determine its severity and the appropriate response protocol.

In the event of an adverse event, it will be assessed to determine its severity and whether it requires additional medical attention or poses a risk to the participant's safety. If necessary, the participant will be referred to receive specific treatment. Finally, their continuation in the intervention will be evaluated.

All identified adverse events will be documented in the study's official registry.

8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

8.3.1 DEFINITION OF ADVERSE EVENTS

This protocol uses the definition of Adverse Event established in 21 CFR 312.32(a):

"Any unintended medical occurrence in a clinical study participant, associated with the use of the investigational intervention, regardless of whether it is causally related to it."

In this specific case, the Adverse Events that may be observed include:

- Physical symptoms.
- Hypoglycemia/Hyperglycemia.
- Physical discomfort.
- Metabolic disturbances.

Although this study is not expected to have a high incidence of Adverse Events due to its nature, any notable event will be documented and evaluated by the research team.

8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS

In this protocol, a Serious Adverse Event (SAE) is defined as any occurrence that involves:

- Patient death.
- Risk to the patient's health or physical integrity.
- Hospitalization.
- Any other medical event resulting from the intervention.

Given the nature of the intervention, the occurrence of Serious Adverse Events is not expected during the course of the study.

8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

8.3.3.1 SEVERITY OF EVENT

For adverse events (AEs) not included in the grading system defined in the protocol, the following guidelines will be used to describe severity:

- **Mild**: Events require minimal or no treatment and do not interfere with the participant's daily activities.
- **Moderate**: Events result in a low level of inconvenience or concern with therapeutic measures. Moderate events may cause some interference with functioning.
- **Severe**: Events disrupt the participant's usual daily activities and may require systemic pharmacological treatment or other interventions. Severe events are often potentially life-threatening or disabling. It should be noted that the term "severe" does not necessarily equate to "serious."

8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION/EXPERIMENTAL MANIPULATION

All adverse events (AEs) will have their relationship to study procedures, including the intervention, assessed by a qualified clinical professional, based on temporal association and clinical judgment. The degree of certainty regarding causality will be classified using the following categories:

- **Related** – The AE is known to occur with study procedures, there is a reasonable possibility that the study procedures caused the AE, or there is a temporal relationship between the study procedures and the event. "Reasonable possibility" means there is evidence suggesting a causal relationship between the study procedures and the AE.
- **Not Related** – There is no reasonable possibility that the study procedures caused the event, there is no temporal relationship between the study procedures and the onset of the event, or an alternative etiology has been established.

8.3.3.3 EXPECTEDNESS

A clinical professional with appropriate experience in type 2 diabetes (T2DM) from the Endocrinology Department of Hospital de Mar, Barcelona, and external to the intervention, will be responsible for determining whether an adverse event (AE) is expected or unexpected. An AE will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the previously described risk information for the study procedures.

8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

All procedures and events occurring in the patients will be recorded. These records will be made every 15 days, coinciding with the scheduled follow-up visits of the intervention. The classification of the type of event will be carried out by a clinician external to the intervention, who can independently assess the severity of the event.

All adverse events occurring at any time after obtaining informed consent will be recorded, up to 7 days after the study completion for mild adverse events, or up to 30 days for serious adverse events. At each study visit, the investigator will inquire about the occurrence of adverse or serious adverse events since the last visit. Events will be followed up to obtain information on outcomes until resolution or stabilization.

For each identified event, the symptoms, onset date, duration of symptoms (if applicable), and any required treatment will be documented. Any deterioration or change in the patient's baseline conditions, both related to T2DM and other comorbidities, will also be recorded as an adverse event.

8.3.5 ADVERSE EVENT REPORTING

All information related to an adverse event will be recorded both in the patient's shared medical record and in the study's official registry.

The person responsible for recording will be the investigator conducting the follow-up calls or the professional performing the examinations scheduled in the protocol.

Once an adverse event has been identified, it will be reported to the principal investigator of the intervention to assess the feasibility of the patient continuing in the study. In addition, the patient's primary care physician will be contacted to evaluate the necessary treatment. This assessment will be carried out within a maximum of 5 days.

8.3.6 SERIOUS ADVERSE EVENT REPORTING

Serious adverse events (SAEs) will be recorded both in the patient's shared medical record and in the study's official registry. The person responsible for recording will be the investigator

conducting the follow-up calls or the professional performing the examinations scheduled in the protocol.

Once a serious adverse event has been identified, it will be reported to the principal investigator of the intervention, who will assess the feasibility of the patient continuing in the study.

Additionally, the patient's primary care physician will be contacted to evaluate the patient's health status and determine the appropriate treatment. In cases of severe urgency, an emergency physician will be contacted. This referral will be made within 24 hours of reporting the event.

8.3.7 REPORTING EVENTS TO PARTICIPANTS

All adverse events and unexpected findings regarding the patients' health status will be communicated. This information will be conveyed privately and individually to each patient, either via telephone contact or during the scheduled follow-up visits with their primary care physician.

8.3.8 EVENTS OF SPECIAL INTEREST

No events of special interest, other than those previously described in the protocol, have been identified.

8.3.9 REPORTING OF PREGNANCY

In the event that a pregnancy is identified in any participant, the situation will be appropriately communicated to the patient. Subsequently, the participant's health status will be documented in the study's official registry. As previously indicated, pregnancy constitutes an exclusion criterion in this study, and participation in the intervention will be immediately discontinued.

8.4 UNANTICIPATED PROBLEMS

8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS

This protocol uses the definition of Unanticipated Problems as established by the Office for Human Research Protections (OHRP). The OHRP considers unanticipated problems involving risks to participants or others to generally include any incident, experience, or outcome that meets all of the following criteria:

- Unexpected in terms of its nature, severity, or frequency, taking into account: (a) the study procedures described in protocol-related documents, such as the protocol approved by the Research Ethics Committee and the informed consent document; and (b) the characteristics of the participant population being studied;
- Related or possibly related to participation in the research (where "possibly related" means there is a reasonable possibility that the incident, experience, or outcome was caused by

the study procedures); and suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than previously known or recognized.

8.4.2 UNANTICIPATED PROBLEMS REPORTING

The principal investigator will be responsible for reporting any unanticipated problem to the responsible entity, Parc Sanitari Pere i Virgili. The report of the problem will include:

- Study identification information
- Detailed description of the incident
- Justification for why it is considered an unanticipated problem
- Description of the proposed protocol changes or corrective measures adopted in response

The deadlines for reporting incidents are as follows:

- Unanticipated problems that constitute serious adverse events (SAEs) will be reported to Parc Sanitari Pere i Virgili within a maximum of 10 days from the investigator becoming aware of the event.
- Any other unanticipated problem will be reported within no more than 15 days.

8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Patients will be informed if an unanticipated problem occurs and poses any risk to them. They will be notified individually if the unanticipated problem affects a specific patient; otherwise, they will be informed collectively if the problem affects the entire group. Notification will be made via telephone contact, by letter, or, if necessary, through a meeting with all participants in the intervention.

9 STATISTICAL CONSIDERATIONS

9.1 STATISTICAL HYPOTHESES

Primary Endpoint:

The primary hypothesis is based on the null hypothesis (H0), which states that there is no difference in the percentage of type 2 diabetes (T2DM) remission between the intervention group and the control group. Conversely, the alternative hypothesis (H1) states that the percentage of T2DM remission will be significantly higher in the intervention group compared to the control group. An efficacy analysis is planned and will be evaluated right after the end of the intervention.

Secondary Endpoints:

The null hypothesis (H0) states that there will be no significant differences in the proposed secondary variables (metabolic, behavioral, and quality-of-life variables) between the intervention group and the control group. Conversely, the alternative hypothesis (H1) states that there will be statistically significant differences in the proposed secondary variables (metabolic, behavioral, and quality-of-life variables), with more favorable outcomes for the intervention group compared to the control group. An efficacy analysis of the intervention is planned, and the evaluation will be carried out 12 months after the end of the intervention.

9.2 SAMPLE SIZE DETERMINATION

Based on the primary variable of the intervention, the percentage of T2DM remission, the required sample size has been calculated to observe statistically significant differences. This variable will be coded dichotomously. A total of 120 volunteers (60 per arm) will be recruited for the study. Accepting an alpha risk of 0.05 (5%) and a beta risk of less than 0.2 in a two-sided test, at least 52 subjects in the control group and 52 subjects in the intervention group would be required to detect as statistically significant a 20% difference between two proportions (primary endpoint: T2DM remission). For the control group, the expected remission rate ranges from 0 to 5%, whereas in the intervention group, it is expected to be at least 25%. The remission rates have been benchmarked against previous studies (Lean et al., n.d.). An estimated loss to follow-up rate of 15% has been considered.

Given the estimated 15% loss to follow-up, the sample size has been increased to 60 participants instead of 52. This ensures that the statistical power of the analysis will be preserved.

9.3 POPULATIONS FOR ANALYSES

The populations identified to be included in the study are as follows:

Intention-to-Treat (ITT) Analysis: All randomized participants who have completed the minimum required follow-up and for whom clinical data and questionnaires are available at baseline (T0), 6 months post-intervention (T-6 months), and 18 months post-intervention (T-18 months).

Per-Protocol Analysis: Participants who have completed at least the main intervention session and for whom clinical data and questionnaires are available at a minimum of baseline (T0) and 6 months post-intervention (T-6 months).

Sensitivity Analysis: Sensitivity analyses will be performed in subgroups according to participant characteristics, including population with more than five years since T2DM diagnosis, sex, and age.

9.4 STATISTICAL ANALYSES

9.4.1 GENERAL APPROACH

The statistical analysis will consist of two sub-analyses. First, a descriptive analysis will be performed, followed by an analysis to determine differences between the intervention and control groups. These analyses will be conducted using STATA/MP statistical software.

In the initial descriptive analysis, qualitative variables (e.g., sex, socioeconomic status) will be described using absolute and relative frequencies. Continuous variables (e.g., age, HbA1c, weight, BMI, blood pressure, cholesterol, HOMA-IR) will be described using mean and standard deviation for normally distributed variables, or median and interquartile range for variables with non-normal distributions. Normality of quantitative variables will first be assessed using the Kolmogorov-Smirnov test. Group comparability will be assessed using standardized mean differences (SMD), with SMD < 0.10 indicating negligible imbalance and SMD ≥ 0.20 indicating meaningful imbalance. Formal hypothesis testing at baseline will not be routinely performed; if included, such p-values will be reported as descriptive only.

The primary efficacy analysis will use analysis of covariance (ANCOVA), with the 6-month value of the primary outcome as the dependent variable and the baseline value as a covariate. The model will include prespecified covariates: baseline outcome, age, sex, site (if applicable), and block/stratum used in randomization. The primary result will be the adjusted mean difference between intervention and control. Absolute risk reduction, relative risk reduction, and number needed to treat will also be calculated.

The secondary efficacy analysis will be a longitudinal analysis. The effect of the intervention in terms of T2DM reversal or remission (dichotomous variable) will be estimated using a mixed-effects model for repeated measures (MMRM) with a random intercept for participant and fixed effects for time, group, and group × time interaction.

All statistical tests will be two-sided, with a significance level of $\alpha = 0.05$ considered statistically significant.

9.4.2 ANALYSIS OF THE PRIMARY ENDPOINT(S)

The primary endpoint is the change in glycated hemoglobin (HbA1c, %) from baseline to 6 months. HbA1c is measured as a continuous variable on an interval scale. The endpoint will be calculated as the absolute difference between baseline HbA1c and the value obtained at 6 months.

The primary analysis will be performed using analysis of covariance (ANCOVA) with treatment group (intervention vs. control) as the fixed factor, and baseline HbA1c as a covariate to improve precision. Additional prespecified covariates will include age, sex, study site, and randomization block, based on their potential clinical relevance and to ensure adjustment for any residual imbalance despite randomization. A secondary, confirmatory analysis will be conducted using a

mixed-effects model for repeated measures (MMRM), which includes all available timepoints (baseline, 3 months, and 6 months). This model accounts for within-subject correlation by specifying an unstructured covariance matrix.

Results will be presented as adjusted mean differences between groups with 95% confidence intervals and corresponding two-sided p-values. Least-squares means (LSMEANS) will be used to report group means adjusted for covariates.

The Intention-to-Treat (ITT) population will be the primary analytic set, including all randomized participants according to their allocated group. A Per-Protocol (PP) population, defined as participants with at least 70% adherence to the intervention, will be analyzed as a sensitivity approach.

Handling of Missing Data; for ANCOVA, missing data at 6 months will be addressed using multiple imputation under the missing-at-random (MAR) assumption. In MMRM, missing data are implicitly handled under MAR. Additional sensitivity analyses will explore the robustness of results to different missing-data mechanisms.

For ANCOVA, residuals will be checked for normality and homoscedasticity. If these assumptions are substantially violated, transformations or nonparametric methods will be considered. For MMRM, model fit will be evaluated and alternative covariance structures tested.

9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The secondary endpoint is diabetes remission at 18 months, defined as achieving HbA1c <6.5% without glucose-lowering medications. It will be analyzed using a generalized linear mixed-effects model (GLMM) with a logit link, including treatment group, time, and group × time interaction as fixed effects, and a random intercept for participants to account for repeated measurements. Prespecified covariates include baseline HbA1c, age, sex, site, and randomization block. Results will be reported as adjusted odds ratios with 95% confidence intervals and two-sided p-values.

The analysis will follow the Intention-to-Treat (ITT) principle; a Per-Protocol (PP) analysis (adherence ≥70%) will be performed as sensitivity. Missing data will be handled under the missing-at-random assumption, with multiple imputation applied if necessary. Trajectories of remission probabilities over time will also be presented.

Others secondary endpoints include:

- Change in body weight (kg) from baseline to 6 months (continuous, interval scale).
- Change in blood pressure (systolic and diastolic, mmHg) from baseline to 6 months (continuous, interval scale).
- Change in lipid profile (total cholesterol, LDL-C, HDL-C, triglycerides, mg/dL) from baseline to 6 months (continuous, interval scale).
- Change in circadian rhythm regularity (measured via validated questionnaire scores; ordinal/interval scale).

- Change in health-related quality of life (measured via validated scale, e.g., SF-12 or equivalent; interval scale).
- Intervention adherence (measured as percentage of scheduled sessions completed; continuous, but categorized as adherent ≥70% vs. non-adherent for analysis).

The analysis models for continuous outcomes (e.g., weight, blood pressure, lipid levels, quality of life scores) will be analyzed using ANCOVA with treatment group as a fixed factor and baseline values as covariates. Repeated measures across timepoints (baseline, 3 months, 6 months) will be analyzed with MMRM to account for within-participant correlations.

For binary/categorical outcomes (e.g., adherence ≥70%, achievement of HbA1c <6.5%) will be analyzed using logistic regression, adjusted for prespecified covariates.

For ordinal outcomes (e.g., circadian rhythm scores if treated as ordinal), ordinal logistic regression will be considered.

All analyses will adjust for baseline values of each outcome, plus prespecified covariates such as age, sex, and site. Covariate selection will be guided by clinical relevance and baseline comparability, aiming for a parsimonious model.

Results will be reported as adjusted mean changes with standard errors (for continuous outcomes), odds ratios with 95% confidence intervals (for binary/ordinal outcomes), and associated p-values. For binary endpoints, absolute risk differences and numbers-needed-to-treat (NNT) will also be reported when applicable.

The same approach as for the primary endpoint will be applied: MMRM for repeated measures (implicitly handling missing values under MAR) and multiple imputation for single-timepoint ANCOVA analyses. Sensitivity analyses will evaluate the robustness of results.

Normality and homoscedasticity will be checked for continuous outcomes. Logistic regression models will be checked for linearity in the logit and absence of multicollinearity. Ordinal models will be checked for proportional odds assumption.

9.4.4 SAFETY ANALYSES

"N/A"

9.4.5 BASELINE DESCRIPTIVE STATISTICS

Baseline descriptive analysis of the study population will include the following: qualitative variables (sex, socioeconomic status, etc.) will be described using absolute and relative frequencies. Continuous variables (age, HbA1c, weight, BMI, blood pressure, cholesterol, HOMA-IR, etc.) will be described as mean and standard deviation for normally distributed data, or as median and interquartile range for non-normally distributed data. Normality of quantitative variables will be assessed using the Kolmogorov-Smirnov test.

Group comparability will be assessed using standardized mean differences (SMD), with SMD < 0.10 indicating negligible imbalance and SMD ≥ 0.20 indicating meaningful imbalance. Formal hypothesis testing at baseline will not be routinely performed; if included, such p-values will be reported as descriptive only.

9.4.6 PLANNED INTERIM ANALYSES

"N/A"

9.4.7 SUB-GROUP ANALYSES

Pre-specified subgroup analyses will be conducted to explore potential heterogeneity of the intervention effect. Subgroups include: age, sex, and duration of DM2.

For each subgroup, the primary and relevant secondary endpoints will be analyzed using the same statistical models as in the main analyses, including the corresponding interaction term between treatment group and subgroup factor. Results will be presented as adjusted effect estimates with 95% confidence intervals and two-sided p-values.

Subgroup analyses are exploratory; no formal adjustment for multiplicity will be applied. Findings will be interpreted cautiously, primarily to generate hypotheses about differential treatment effects across subgroups.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Individual participant data will be listed in tabular form by measure and time point in the study database and for reporting purposes. Each participant's measurements for primary and secondary endpoints, as well as adherence and safety outcomes, will be recorded at all scheduled visits. These tables will be used for internal review, data verification, and regulatory reporting, but will not be published with identifiable participant information.

9.4.9 EXPLORATORY ANALYSES

See 9.4.7 Sub-Group Analyses.

10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATIONS

10.1.1 INFORMED CONSENT PROCESS

10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Informed consent and required documentation will be obtained from participants prior to the initiation of the intervention. Potential participants to be included in the study will be informed about its objectives, implications, schedule, and duration. If they agree to participate, they will be provided with the information sheet and the informed consent form to be signed. At any time, participants may consult with a member of the research team for any questions or clarifications. Once informed consent has been obtained, they may be included in the study.

The information sheet and informed consent form to be provided to all participants are attached, available in Catalan and Spanish (the official languages of the study region).

No external recruitment materials will be used, as invitations will be extended directly by the primary care professionals responsible for the patients.

10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

The CAP Larard, CAP Vila Olímpica and CAP Barceloneta, belonging to the Parc Sanitari Pere Virgili (Carrer d'Esteve Terradas, 30, Gràcia, 08023 Barcelona), are responsible for the appropriate management of the data and commit to adhering to the principles of the Declaration of Helsinki (Fortaleza, Brazil, October 2013), Good Clinical Practice, and applicable data protection regulations, including EU Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016 on Data Protection (General Data Protection Regulation – GDPR), Organic Law 3/2018, as well as all applicable Spanish and European regulations on privacy and personal data protection.

The study will be conducted in accordance with the protocol reviewed by the Research Ethics Committee on Medicinal Products (CEIm) of Parc de Salut Mar, Barcelona, with registration number 2025/12023/I. (The final assessment report from CEIm Parc Salut Mar, Barcelona is attached).

If participants agree to take part in the study, they will be provided with the information sheet and the informed consent form to be signed (see Attached Documents 1 and 2). Participants will have a period of time to reflect on their decision and may consult members of the research team at any time to resolve any questions before signing the informed consent form. Study materials will be provided in Catalan and Spanish.

This study does not include consent by a legal representative, as no minors or individuals with cognitive impairment or who are legally incapacitated will be enrolled.

10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if reasonable grounds justify such a decision. Written notification, documenting the reasons for the suspension or termination, will be provided by the responsible party to the participants and to Parc Sanitari Pere Virgili.

In the event of suspension or early termination, the principal investigator will immediately inform the study participants and Parc Sanitari Pere Virgili of the reasons for the decision. Participants will be contacted to communicate any changes in visit scheduling or other implications related to their participation.

Circumstances that may justify temporary suspension or early termination of the study include, but are not limited to:

- Identification of unexpected, significant, or unacceptable risks to participants.
- Early evidence of efficacy warranting study interruption.
- Major protocol deviations by the research team.
- Incomplete or non-evaluable data preventing the validity of results.
- Determination that the study's primary endpoint has been achieved.
- Determination of futility of the study.

The study may be resumed once concerns regarding safety, protocol compliance, and data quality have been adequately addressed and resolved, and provided that approval is granted by Parc Sanitari Pere Virgili.

10.1.3 CONFIDENTIALITY AND PRIVACY

This study will be conducted in strict compliance with Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data (General Data Protection Regulation – GDPR), as well as with Organic Law 3/2018 of 5 December on the Protection of Personal Data and Guarantee of Digital Rights.

Pseudo-anonymization of data will be implemented to ensure the confidentiality of participants' personal information. Each participant will be assigned an identification number to associate all data collected throughout the study. The link between the identification number and the personal data will be kept exclusively by the principal investigator.

Data storage will ensure integrity, traceability, and appropriate preservation for the established period (maximum 5 years after the study). Under no circumstances will the data be partially or fully removed.

Data will be stored on the internal network units of Parc Sanitari Pere i Virgili with restricted access for the research team, and in the Data Protection Officer (DPO) unit of Parc Sanitari Pere i Virgili with password-protected access.

All data collected during the study will be anonymized and stored in REDCap (Research Electronic Data Capture). The REDCap platform provides a secure environment for data storage and supports all stages of the study, from administering questionnaires and scales to participants to storage and subsequent analysis.

No data will be removed or disclosed at any point during the study. If it becomes necessary to share information with third parties (e.g., for external statistical analysis), the data will be fully anonymized.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Biological samples will be obtained as part of routine clinical care, and the resulting data will be used for the study.

For each participant, the biological samples collected throughout the study will include:

- Number and type of samples: Three blood samples and three urine samples will be collected.
- Timing of collection: Samples will be obtained at the start of the intervention, 6 months post-intervention, and 18 months post-intervention.
- Processing and analysis methods: Blood samples will be collected by venipuncture using standard clinical practice procedures in primary care, obtaining the minimum volume necessary, and stored in sealed tubes. Urine samples will be collected by providing the participant with a sterile container to collect the first morning urine, which will then be retrieved by healthcare personnel. Both blood and urine samples will be processed in an external laboratory.
- Analysis location: Sample collection will take place at the participant's reference CAP (CAP Larrard or CAP Barceloneta).
- Sample disposition: Once the project analyses are completed, all samples will be destroyed according to the standard protocols of the analysis laboratory.
- Sample coding: Samples will be labeled with barcodes and alphanumeric codes, each linked to the participant's healthcare identification number.

The storage of biological samples for future research after the study is not planned.

Clinical data and questionnaires collected during the study will be anonymized and stored in the REDCap (Research Electronic Data Capture) platform, hosted on the secure servers of Parc Sanitari Pere Virgili (PSPV). Data will be retained for a maximum of 5 years after study completion and will not be shared with third parties.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

Principal investigator
Alexandre Ternianov
Physician specialist in Family and Community Care
Parc Sanitari Pere Virgili, Barcelona
Primary and Community Care Research Group in Barcelona (APICBA), Hospital del Mar Research Institute
Tel: 932 21 37 85
e-mail: aternianov@perevirgili.cat

Collaborating investigators
Neus Carrilero Carrió
Primary and Community Care Research Coordinator, Parc Sanitari Pere Virgili
Primary and Community Care Research Group in Barcelona (APICBA), Hospital del Mar Research Institute
Tel: 659 77 29 79
e-mail: ncarrilero@perevirgili.cat

Sonia Moreno Escribà
Physician specialist in Family and Community Care
Parc Sanitari Pere Virgili, Barcelona
Primary and Community Care Research Group in Barcelona (APICBA), Hospital del Mar Research Institute
e-mail: smorenoe@perevirgili.cat

Anna Parellada Roura
Dietitian-Nutritionist
Parc Sanitari Pere Virgili, Barcelona
e-mail: aparellada@perevirgili.cat

Vanina Andrés Troyas
Physician
Parc Sanitari Pere Virgili, Barcelona
e-mail: vandrest@perevirgili.cat

José Javier Vega Córdova
Resident Physician specializing in Family and Community Care
Parc Sanitari Pere Virgili, Barcelona
e-mail: jvega@perevirgili.cat

Giulia Satu Faini
Resident Physician specializing in Family and Community Care
Parc Sanitari Pere Virgili, Barcelona
e-mail: gfaini@perevirgili.cat

Jesse Omar Anagua Melendres
Resident Physician specializing in Family and Community Care
Parc Sanitari Pere Virgili, Barcelona
e-mail: janagua@perevirgili.cat

Luis Adrian Soto Mota
Internist (Specialist in Internal Medicine)
Metabolic Diseases Research Unit, National Institute of Medical Sciences and Nutrition Salvador
e-mail: adrian.soto@tec.mx

The study is overseen by a Steering Committee responsible for the design, conduct, and reporting of the trial. Operational activities (data collection, monitoring, statistical analysis) are managed by the study team, including coordinators, data managers, and statisticians. Safety and ethical oversight is provided by the Ethics Committee (CEIm, Hospital del Mar, Barcelona).

Key roles include Principal Investigator, Co-investigators, Study Coordinators, Data Management Team, and Statistical Team. Any suspected misconduct by staff can be reported to the institutional research office or Ethics Committee. Participants are informed in the consent form of their right to contact the Ethics Committee with concerns.

10.1.6 SAFETY OVERSIGHT

Due to the non-pharmacological nature of the intervention, it is considered low risk for participants. Therefore, safety oversight will be managed by the research team, who will be responsible for identifying and reporting any adverse events that occur. The internal safety monitoring plan outlined in this protocol consists of periodic meetings of the research team, during which any incidents arising from the intervention will be discussed, and adherence to the defined protocol and Good Clinical Practice will be evaluated.

Any adverse event identified will be recorded and reported to the participant, the Principal Investigator, and Parc Sanitari Pere i Virgili. In the case of repeated serious adverse events, the situation will be urgently assessed, and if necessary, the intervention may be considered for temporary suspension.

The creation of an independent Data Safety Monitoring Board (DSMB) is not planned, as the type of intervention and the risk profile of the study do not require it.

10.1.7 CLINICAL MONITORING

Due to the low-risk nature of the intervention, independent external clinical monitoring is not planned. Compliance with this protocol, as well as oversight of the proper conduct of the study, will be the responsibility of the research team. They will ensure correct data collection, adherence to the protocol, participant safety, and compliance with Good Clinical Practice and other applicable regulations.

Self-monitoring activities, as well as data quality control and quality assurance procedures, are described in section 10.1.8, Quality Assurance and Quality Control. A separate Clinical Monitoring Plan (CMP) is not required, and no independent external audits are anticipated.

10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Both quality assurance and quality control of the study will be the responsibility of the research team. The internal procedures to be followed are as follows:

Quality Control:

- Informed Consent: Verification of proper completion of the informed consent forms. The research team will ensure that all participants' signed consent forms are properly collected and stored.
- Clinical Data and Questionnaires: All data collected during the intervention sessions, validated questionnaires, and electronic records (in this case using the eCAP program, the shared electronic health record system used by healthcare professionals at primary care centers) will be entered into the REDCap database, which provides a secure environment for data storage. Random checks between source documents and the database will be performed to ensure accurate data entry.
- Biological Samples: Both blood and urine samples will be obtained using standard clinical practice procedures in primary care and subsequently processed in an external laboratory. Samples will be coded using barcodes and alphanumeric codes, each linked to the participant's healthcare identification number. To ensure proper handling, traceability checks will be performed, following the samples from collection through processing at the external laboratory.

Additionally, the quality of the intervention will be ensured through:

- Rigorous and specific training of intervention personnel: Staff will receive training on the protocol and proper data collection procedures.
- Monitoring adherence to the intervention protocol: Compliance with the intervention procedures will be regularly assessed. Any incidents detected will be documented, reported, and evaluated.

10.1.9 DATA HANDLING AND RECORD KEEPING

10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

Data collection will be the responsibility of the clinical and research staff at the participating centers, under the supervision of the Principal Investigator. The Principal Investigator will ensure the accuracy, completeness, legibility, and timeliness of all data recorded in the study.

Data will be collected through a combination of paper source documents (such as self-administered questionnaires, clinical records, and sample collection forms) and the eCAP program, the shared electronic health record system used by healthcare professionals at primary care centers during patient visits. All data will be entered into the REDCap database, which provides a secure environment for data storage and requires user authentication with a username and password.

Biological samples will be labeled with non-identifiable alphanumeric codes and managed by collaborating clinical laboratories. Analytical results will be entered into the REDCap database by the research team.

All data will be handled in accordance with current personal data protection regulations (Regulation (EU) 2016/679 and Organic Law 3/2018) and will be retained for a minimum of 5 years after study completion, in accordance with applicable law.

10.1.9.2 STUDY RECORDS RETENTION

All study documents (protocol, informed consent forms, etc.) will be retained for a minimum of 5 years after study completion, in accordance with Good Clinical Practice (ICH-GCP) guidelines.

Documents will not be destroyed without prior written consent from Parc Sanitari Pere i Virgili or the relevant regulatory authority.

All documentation will be stored securely, protected against unauthorized access, and in compliance with current personal data protection regulations (Regulation (EU) 2016/679 and Organic Law 3/2018).

10.1.10 PROTOCOL DEVIATIONS

This protocol defines a deviation as any non-compliance with the approved protocol or Good Clinical Practice (GCP) standards. Deviations may originate from participants, site staff, or the Principal Investigator and must be documented, reviewed, and reported in accordance with applicable ethical and regulatory requirements.

Protocol deviations are not permitted, except when necessary to eliminate an immediate risk to a participant. If a deviation occurs, it will be recorded in the official study record, evaluated by the research team, and reported to Parc Sanitari Pere i Virgili.

10.1.11 PUBLICATION AND DATA SHARING POLICY

Publication and sharing policy wil be as follow: this trial will be registered on ClinicalTrials.gov, and information on the results will be submitted to this platform. In addition, every effort will be made to publish the results in peer-reviewed scientific journals. Data derived from this study may be requested by other researchers máximum 5 years after completion of the primary endpoint, by contacting Parc Sanitari Pere i Virgili. Considerations to ensure the confidentiality of these shared data are described in Section 10.1.3.

10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any real or perceived influence, such as that of the pharmaceutical industry, is essential. Therefore, any actual conflict of interest of individuals involved in the design, conduct, analysis, publication, or any other aspect of this trial will be disclosed and managed. In addition, individuals with a perceived conflict of interest must undergo appropriate management in accordance with their participation in the study's design and development. The study leadership, together with Parc Sanitari Pere i Virgili, has established policies and procedures to ensure that all members of the study team disclose any conflicts of interest and has implemented a mechanism to manage all reported dualities of interest.

10.2 ADDITIONAL CONSIDERATIONS

In this protocol, no additional considerations are anticipated beyond those already described above.

10.3 ABBREVIATIONS AND SPECIAL TERMS

ADA	American Diabetes Association
AE	Adverse Event
ALT	Alanine Aminotransferase
SMBP	Self-Measured Blood Pressure
PC	Primary Care
Apo B100	Apolipoprotein B100
AST	Aspartate Aminotransferase
CAP	Centro Atención Primaria (Primary Care Center)
DDD	Defined Daily Dose
T2DM	Type 2 Diabetes Mellitus

GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
ITT	Intention-To-Treat
HbA1c	Glycated Hemoglobin
HDL	High Density Lipoprotein
AH	Arterial Hypertension
BMI	Body Mass Index
LDL	Light Density Lipoprotein
NAFLD	Nonalcoholic fatty liver disease
IHC	Individual Health Card
QA	Quality Assurance
QC	Quality Control
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SA	Schedule of Activities

10.4 PROTOCOL AMENDMENT HISTORY

*The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A **Summary of Changes** table for the current amendment is located in the **Protocol Title Page**.*

Version	Date	Description of Change	Brief Rationale

11 REFERENCES

- Alexander CM, Landsman PB, Teutsch SM, Haffner SM. NCEP-defined metabolic syndrome, diabetes, and prevalence of coronary heart disease among NHANES III participants age 50 years and older. Diabetes [Internet]. 2003 May 1 [cited 2024 Nov 6];52(5):1210–4. Available from: https://pubmed.ncbi.nlm.nih.gov/12716754/
- Alonso J, Prieto L, Antó JM. [The Spanish version of the SF-36 Health Survey (the SF-36 health questionnaire): an instrument for measuring clinical results]. Med Clin (Barc). 1995 May;104(20):771–6.
- American Diabetes Association Professional Practice Committee. 5. Facilitating Behavior Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S60-S82. doi: 10.2337/dc22-S005. PMID: 34964866.
- American Diabetes Association Professional Practice Committee. 6. Glycemic Targets: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022 Jan 1;45(Suppl 1):S83-S96. doi: 10.2337/dc22-S006. PMID: 34964868.
- Angulo P, Hui JM, Marchesini G, Bugianesi E, George J, Farrell GC, et al. The NAFLD fibrosis score: a noninvasive system that identifies liver fibrosis in patients with NAFLD. Hepatology [Internet]. 2007 Apr [cited 2024 Nov 6];45(4):846–54. Available from: https://pubmed.ncbi.nlm.nih.gov/17393509/
- Association AD. 2. Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes—2021. Diabetes Care [Internet]. 2021 Jan 1 [cited 2024 Nov 6];44(Supplement_1):S15–33. Available from: https://dx.doi.org/10.2337/dc21-S002
- Association AD. Standards of Medical Care in Diabetes—2022 Abridged for Primary Care Providers. Clinical Diabetes. 2022 Jan 1;40(1):10–38.
- Athinarayanan SJ, Adams RN, Hallberg SJ, McKenzie AL, Bhanpuri NH, Campbell WW, et al. Long-term effects of a novel continuous remote care intervention including nutritional ketosis for the management of type 2 diabetes: A 2-year nonrandomized clinical trial. Front Endocrinol (Lausanne). 2019;10(JUN).
- Bhanpuri NH, Hallberg SJ, Williams PT, McKenzie AL, Ballard KD, Campbell WW, et al. Cardiovascular disease risk factor responses to a type 2 diabetes care model including nutritional ketosis induced by sustained carbohydrate restriction at 1 year: An open label, non-randomized, controlled study. Cardiovasc Diabetol. 2018;17(1):1–16.
- Block G. A review of validations of dietary assessment methods. Am J Epidemiol. 1982 Apr;115(4):492–505.
- Burke LE, Wang J, Sevick MA. Self-monitoring in weight loss: a systematic review of the literature. J Am Diet Assoc. 2011 Jan;111(1):92-102. doi: 10.1016/j.jada.2010.10.008. PMID: 21185970; PMCID: PMC3268700.
- Cálculo: Cuantificación del consumo de alcohol - Fisterra [Internet]. [cited 2024 Oct 28]. Available from: https://www.fisterra.com/ayuda-en-consulta/calculos/cuantificacion-consumo-alcohol/
- CDC. Cancers Associated with Overweight and Obesity Make up 40 percent of Cancers Diagnosed in the United States. 2017.

- Committee ADAPP. 5. Facilitating Behavior Change and Well-being to Improve Health Outcomes: Standards of Medical Care in Diabetes—2022. Diabetes Care. 2021 Dec 16;45(Supplement_1):S60–82.
- Crespo C, Brosa M, Soria-juan A, Lopez-alba A, López-Martínez N, Soria B. Costes directos de la DM y de sus complicaciones en España. Estudio SECCAID. Avances en diabetología. 2015;29(6):182–9.
- Dyńka D, Rodzeń Ł, Rodzeń M, Łojko D, Kraszewski S, Ibrahim A, et al. Beneficial Effects of the Ketogenic Diet on Nonalcoholic Fatty Liver Disease (NAFLD/MAFLD). J Clin Med. 2024 Aug 17;13(16):4857.
- Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998 Sep;352(9131):854–65.
- ElSayed NA, Aleppo G, Aroda VR, Bannuru RR, Brown FM, Bruemmer D, et al. 5. Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes: Standards of Care in Diabetes—2023. Diabetes Care [Internet]. 2022 Dec 12;46(Supplement_1):S68–96. Available from: https://doi.org/10.2337/dc23-S005
- Evert AB, Dennison M, Gardner CD, Timothy Garvey W, Karen Lau KH, MacLeod J, et al. Nutrition therapy for adults with diabetes or prediabetes: A consensus report. Diabetes Care. 2019;42(5):731–54.
- Fanelli MT, Stevenhagen KJ. Consistency of energy and nutrient intakes of older adults: 24-hour recall vs. 1-day food record. J Am Diet Assoc. 1986 May;86(5):665–7.
- Freedman LS, Commins JM, Willett W, Tinker LF, Spiegelman D, Rhodes D, et al. Evaluation of the 24-Hour Recall as a Reference Instrument for Calibrating Other Self-Report Instruments in Nutritional Cohort Studies: Evidence From the Validation Studies Pooling Project. Am J Epidemiol. 2017 Jul 1;186(1):73–82.
- Friedman, Lawrence M., Curt D. Furberg, David L. DeMets, David M. Reboussin, and Christopher B. Granger. 2015. Fundamentals of Clinical Trials. Cham: Springer International Publishing. https://doi.org/10.1007/978-3-319-18539-2.
- García-Peñas JJ. Trastornos del espectro autista y epilepsia: El papel de la dieta cetogénica. Rev Neurol. 2016;62(Supl 1):S73–8.
- Gepner Y, Shelef I, Komy O, Cohen N, Schwarzfuchs D, Bril N, et al. The beneficial effects of Mediterranean diet over low-fat diet may be mediated by decreasing hepatic fat content. J Hepatol. 2019;71(2):379–88.
- Gersovitz M, Madden JP, Smiciklas-Wright H. Validity of the 24-hr. dietary recall and seven-day record for group comparisons. J Am Diet Assoc. 1978 Jul;73(1):48–55.
- Gjuladin-Hellon T, Davies IG, Penson P, Baghbadorani RA. Effects of carbohydrate-restricted diets on low-density lipoprotein cholesterol levels in overweight and obese adults: A systematic review and meta-analysis. Nutr Rev. 2019;77(3):161–80.
- Hallberg SJ, McKenzie AL, Williams PT, Bhanpuri NH, Peters AL, Campbell WW, et al. Effectiveness and Safety of a Novel Care Model for the Management of Type 2 Diabetes at 1 Year: An Open-Label, Non-Randomized, Controlled Study. Diabetes Therapy. 2018;9(2):583–612.
- Hambleton I, Guariguata L, Shaw JE, Linnenkamp U, Beagley J, Whiting DR. Global estimates of diabetes prevalence for 2013 and projections for 2035. Diabetes Res Clin Pract. 2013;103(2):137–49.

- Harvey CJDC, Schofield GM, Zinn C, Thornley SJ, Crofts C, Merien FLR. Low-carbohydrate diets differing in carbohydrate restriction improve cardiometabolic and anthropometric markers in healthy adults: A randomised clinical trial. PeerJ. 2019;2019(2).
- Hession M, Rolland C, Kulkarni U, Wise A, Broom J. Systematic review of randomized controlled trials of low-carbohydrate vs. low-fat/low-calorie diets in the management of obesity and its comorbidities. Obesity Reviews. 2009;10(1):36–50.
- HOMA Calculator — Radcliffe Department of Medicine [Internet]. [cited 2024 Oct 28]. Available from: *https://www.rdm.ox.ac.uk/about/our-clinical-facilities-and-units/DTU/software/homa*
- International Diabetes Federation (IDF). The IDF consensus worldwide definition of the metabolic syndrome [Internet]. 2006 [cited 2024 Nov 6]. Available from: https://idf.org/media/uploads/2023/05/attachments-30.pdf
- Jang EC, Jun DW, Lee SM, Cho Y kyun, Ahn SB. Comparison of efficacy of low-carbohydrate and low-fat diet education programs in non-alcoholic fatty liver disease: A randomized controlled study. Hepatology Research. 2018;48(3):E22–9.
- Kotronen A, Peltonen M, Hakkarainen A, Sevastianova K, Bergholm R, Johansson LM, et al. Prediction of non-alcoholic fatty liver disease and liver fat using metabolic and genetic factors. Gastroenterology [Internet]. 2009 [cited 2024 Nov 6];137(3):865–72. Available from: https://pubmed.ncbi.nlm.nih.gov/19524579/
- Lakka HM, Lakka TA, Tuomilehto J, Sivenius J, Salonen JT. Hyperinsulinemia and the risk of cardiovascular death and acute coronary and cerebrovascular events in men: the Kuopio Ischaemic Heart Disease Risk Factor Study. Arch Intern Med. 2000 Apr;160(8):1160–8.
- Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Durability of a primary care-led weight-management intervention for remission of type 2 diabetes: 2-year results of the DiRECT open-label, cluster-randomised trial. Lancet Diabetes Endocrinol. 2019;7(5):344–55.
- Lean MEJ, Leslie WS, Barnes AC, Brosnahan N, Thom G, McCombie L, et al. Primary care-led weight management for remission of type 2 diabetes (DiRECT): an open-label, cluster-randomised trial. The Lancet. 2018 Feb 10;391(10120):541–51.
- López De La Torre M, Bellido Guerrero D, Vidal Cortada J, Soto González A, García Malpartida K, Hernandez-Mijares A. Distribución de la circunferencia de la cintura y de la relación circunferencia de la cintura con respecto a la talla según la categoría del índice de masa corporal en los pacientes atendidos en consultas de endocrinología y nutrición. Endocrinología y Nutrición [Internet]. 2010 Dec 1 [cited 2024 Nov 6];57(10):479–85. Available from: https://www.elsevier.es/es-revista-endocrinologia-nutricion-12-articulo-distribucion-circunferencia-cintura-relacion-circunferencia-S1575092210001737
- Madden JP, Goodman SJ, Guthrie HA. Validity of the 24-hr. recall. Analysis of data obtained from elderly subjects. J Am Diet Assoc. 1976 Feb;68(2):143–7.
- Mantilla Toloza SC, Gómez-Conesa A. El Cuestionario Internacional de Actividad Física. Un instrumento adecuado en el seguimiento de la actividad física poblacional. Revista Iberoamericana de Fisioterapia y Kinesiología [Internet]. 2007 Jan 1 [cited 2024 Oct 28];10(1):48–52. Available from: https://www.elsevier.es/es-revista-revista-iberoamericana-fisioterapia-kinesiologia-176-articulo-el-cuestionario-internacional-actividad-fisica--13107139

- McKenzie AL, Hallberg SJ, Creighton BC, Volk BM, Link TM, Abner MK, et al. A Novel Intervention Including Individualized Nutritional Recommendations Reduces Hemoglobin A1c Level, Medication Use, and Weight in Type 2 Diabetes. JMIR Diabetes. 2017;2(1):e5.
- Nubiola A, Ferrer M, Remolins I. La asociación de hiperinsulinemia con riesgo cardiovascular y cáncer plantea nuevos retos en el abordaje del paciente con diabetes tipo 2, insulinorresistente. Hipertens Riesgo Vasc. 2015;32(1):21–6.
- Paoli A, Rubini A, Volek JS, Grimaldi KA. Beyond weight loss: A review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. Eur J Clin Nutr. 2013;67(8):789–96.
- Rahier J, Guiot Y, Goebbels RM, Sempoux C, Henquin JC. Pancreatic beta-cell mass in European subjects with type 2 diabetes. Diabetes Obes Metab. 2008 Nov;10 Suppl 4:32–42.
- Riddle MC, Cefalu WT, Evans PH, Gerstein HC, Nauck MA, Oh WK, et al. Consensus report: Definition and interpretation of remission in type 2 diabetes. Diabetes Care. 2021 Oct 1;44(10):2438–44.
- Rubins HB, Robins SJ, Collins D, Nelson DB, Elam MB, Schaefer EJ, et al. Diabetes, plasma insulin, and cardiovascular disease: subgroup analysis from the Department of Veterans Affairs high-density lipoprotein intervention trial (VA-HIT). Arch Intern Med. 2002 Dec;162(22):2597–604.
- Rudenski AS, Hadden DR, Atkinson AB, Kennedy L, Matthews DR, Merrett JD, et al. Natural History of Pancreatic Islet B-Cell Function in Type 2 Diabetes Mellitus Studied over Six Years by Homeostasis Model Assessment. Diabet Med. 1988 Jan;5(July 1987):36–41.
- Sainsbury E, Kizirian N V., Partridge SR, Gill T, Colagiuri S, Gibson AA. Effect of dietary carbohydrate restriction on glycemic control in adults with diabetes: A systematic review and meta-analysis. Diabetes Res Clin Pract. 2018;139:239–52.
- Secretan BL, Ph D, Scoccianti C, Ph D, Loomis D, Ph D. Body Fatness and Cancer — Viewpoint of the IARC Working Group. New England Journal of Medicine. 2016;375(8):794–8.
- Soriguer F, Goday A, Bosch-Comas A, Bordiú E, Calle-Pascual A, Carmena R, et al. Prevalence of diabetes mellitus and impaired glucose regulation in Spain: The Di@bet.es Study. Diabetologia. 2012;55(1):88–93.
- Taheri S, Zaghloul H, Chagoury O, Elhadad S, Ahmed SH, El Khatib N, et al. Effect of intensive lifestyle intervention on bodyweight and glycaemia in early type 2 diabetes (DIADEM-I): an open-label, parallel-group, randomised controlled trial. Lancet Diabetes Endocrinol. 2020 Jun;8(6):477–89.
- Tay J, Luscombe-Marsh ND, Thompson CH, Noakes M, Buckley JD, Wittert G. A, et al. Comparison of low- and high-carb diets for T2DM management: A randomized trial. American Journal of Clinical Nutrition. 2015;102(4):780–90.
- U.K. prospective diabetes study 16. Overview of 6 years' therapy of type II diabetes: a progressive disease. U.K. Prospective Diabetes Study Group. Diabetes. 1995 Nov;44(11):1249–58.
- Unwin D, Delon C, Unwin J, Tobin S, Taylor R. What predicts drug-free type 2 diabetes remission? Insights from an 8-year general practice service evaluation of a lower carbohydrate diet with weight loss. BMJ Nutr Prev Health. 2023 Jan 2;e000544.

- Unwin D, Khalid AA, Unwin J, Crocombe D, Delon C, Martyn K, et al. Insights from a GP service evaluation supporting a low carb diet in patients with T2DM and preDM: A secondary analysis of routine clinic data prescribing over 6 years. BMJ Nutr Prev Health. 2020.
- Unwin D, Unwin J, Crocombe D, Delon C, Guess N, Wong C. Renal function in patients following a low carbohydrate diet for type 2 diabetes. Curr Opin Endocrinol Diabetes Obes. 2021;Publish Ah.
- Unwin DJ, Tobin SD, Murray SW, Delon C, Brady AJ. Substantial and sustained improvements in blood pressure, weight and lipid profiles from a carbohydrate restricted diet: An observational study of insulin resistant patients in primary care. Int J Environ Res Public Health. 2019;16(15).
- Valencia-Martín JL, González MJ, Galán I. Methodological issues in the measurement of alcohol consumption: The importance of drinking patterns. Rev Esp Salud Publica. 2014 Aug 1;88(4):433–46.
- Weber DD, Aminazdeh-Gohari S, Kofler B. Ketogenic diet in cancer therapy. Aging. 2018 Feb 11;10(2):164–5.
- Westman EC, Yancy WS, Humphreys M. Dietary treatment of diabetes mellitus in the pre-insulin era (1914-1922). Perspect Biol Med. 2006;49(1):77–83.
- WHOCC. ATC/DDD Index.
- World Health Organisation. "Evidence for Action World Health Organization 2003." https://iris.who.int/bitstream/handle/10665/42682/9241545992.pdf.
- World Health Organization. Global action plan for the prevention and control of NCDs 2013-2020. WHO Document Production Services, Geneva, Switzerland. 2013.
- Yang X, Zhou J, Shao H, Huang B, Kang X, Wu R, et al. Effect of an Intermittent Calorie-restricted Diet on Type 2 Diabetes Remission: A Randomized Controlled Trial. J Clin Endocrinol Metab. 2023 May 17;108(6):1415–24.
- Zabaleta-Del-Olmo E, Casajuana-Closas M, López-Jiménez T, Pombo H, Pons-Vigués M, Pujol-Ribera E, et al. Multiple health behaviour change primary care intervention for smoking cessation, physical activity and healthy diet in adults 45 to 75 years old (EIRA study): a hybrid effectiveness-implementation cluster randomised trial. BMC Public Health. 2021 Dec 4;21(1):2208. doi: 10.1186/s12889-021-11982-4. PMID: 34863136; PMCID: PMC8642878.