Ayuda para el automanejo Integral de la Diabetes MEllitus (AID ME)

Comprehensive Self-Management Aid for Diabetes Mellitus (AID ME)

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Sponsor:

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BACKGROUND

World Health Organization (WHO) rates that more than 346 million people worldwide have diabetes mellitus (DM). This number is likely to more than double by 2030 without any action. WHO also rates that cardiovascular diseases (CVDs) are the leading cause of death globally, taking around 17.9 million lives each year [1].

One of the biggest challenges for health care providers today is addressing the continued needs and demands of individuals with chronic illnesses. The value of regular follow-up of these patients with the health care provider should be noteworthy in eluding any long-term complications. In too many occasions, different studies revealed poor adherence to treatment regimens due among other, to poor attitude towards DM and cardiovascular risk factors and poor health literacy [2].

One response to these challenges is the promotion of self-care via encouraging greater involvement of chronically ill individuals [3]. WHO defines self-care as the ability of individuals, families and communities to promote and maintain their own health, prevent disease, and to cope with illness – with or without the support of a health or care worker [4]. Self-care interventions can include medicines, devices, diagnostics and digital tools. Self-care actions include practices, habits, and lifestyle choices.

In people having DM there are seven crucial self-care behaviours which could anticipate good outcomes and that could be expanded to other CVDs. These are healthy eating, being physically active, monitoring of blood sugar, compliant with medications, good problem-solving skills, healthy coping skills and risk-reduction behaviours (5).

Digital health technologies (DHTs), which include mobile applications (apps) have been rapidly gaining popularity in the self-management of chronic diseases [6]. The use of technology has transformed the approach to diabetes self-care and its implementation. Technology developed to support self-care includes medical devices such as glucose meters, insulin pumps, and continuous glucose monitors; digital therapeutics such as mobile apps, text messaging, electronic communications, and videoconference platforms; and wearable technologies such as Fitbits and smartwatches.

Over the last few years, several studies have been published based on the effects of digital technologies on the approach to both type 1 and type 2 DM, with different results. In some cases,

systematic reviews of these studies have shown positive results [7,8]; However, in others these results have been less conclusive [9,10].

Given the rapid evolution of the devices used, as well as advances in DM treatments, it is true that some of these studies may have become obsolete in a short time. It is therefore clear that differences in study design, intervention group, outcome measures, and the specific functions and characteristics of the technologies under consideration have led to widespread variability in the estimation of the impact of digital technologies on DM. In any case, and despite the application of this methodology to the population for decades, the burden of both DM and cardiovascular diseases has continued to increase. The latest analysis of the "Global Burden of the diseases" published in The Lancet in 2023 [11] indicates that the prevalence of diabetes is increasing worldwide, mainly due to an increase in obesity caused by multiple factors, making it essential to better understand the disparities in risk factor profiles and the burden of diabetes in different populations, in order to base strategies to successfully control diabetes risk factors in the context of multiple and complex factors.

Currently living in an era of digital explosion related to big data and artificial intelligence, these new tools can provide a new push for the development of effective self-management programs for these chronic diseases. For several years now, tools based on artificial intelligence have been developed with high precision in their results in relation to lifestyle modification. For example, based on machine learning algorithms, personalized diets created with the help of an accurate blood glucose response predictor that integrates parameters such as dietary habits, physical activity, and gut microbiota can successfully reduce post-meal blood glucose and its long-term metabolic consequences [12]. We are currently witnessing a validation moment of these generated tools. Following the previous example, this new tool was subsequently evaluated in a pilot study with 23 patients [13] that sought to assess the clinical effects of a personalized postprandial diet based on the AI-created tool on glycemic control and metabolic health in people with newly diagnosed type 2 diabetes compared to the commonly recommended Mediterranean diet. As a result, the personalized diet improved glycemic measurements significantly more than a Mediterranean-style diet. An additional 6-month personalized diet intervention further improved glycemic control and metabolic health parameters, supporting the clinical efficacy of this approach.

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Aware of the burden of the progressive increase in non-communicable diseases (NCD), the European Union (EU) launched a project to try to improve the approach to these pathologies and reduce the burden they represent both for people who suffer from them and for the health systems that care for them.

JACARDI is the Joint Action co-financed by the EU4Health programme of the European Union that provides support to 21 member countries committed to addressing the challenge of CVD and DM and reducing their burden. This collaborative initiative will integrate validated best practices and/or interventions through 142 pilot studies, complementing and reinforcing existing policies and programmes.

The different pilot studies to be carried out cover the entire “patient journey”, from health literacy and awareness of CVD/DM, through screening and primary prevention of high-risk populations, to people living with one of these diseases and their care providers [14]

This pilot project is part of JACARDI. The intervention focuses on self-management of their disease in the context of people living with diabetes, employing the use of new technologies and devices that empower the patient to better self-manage their disease. The project focuses especially on the development of a physical activity program evaluated by an artificial intelligence tool (Kinetikos©, [15]), but will also cover nutritional advice and medication management.

Our working hypothesis is that the application of this tool on an intervention group will improve people's knowledge about their disease and this will have an impact on improvements both in the metabolic control of DM and in the quality of life of the person living with this disease.

AIMS

2.1 – GENERAL OBJECTIVE

2.2 – PRIMARY END-POINT

To decrease glycosylated hemoglobin in the intervention branch by more than 0.5% compared to the control branch.

2.3- SECONDARY END-POINTS

Improve self-management capacity in the intervention branch, mainly focused on aspects related to diet, physical activity and therapeutic adherence. Variations at the beginning and end of follow-up will be considered using different tests designed for this purpose.

Assess whether there are differences in glycemic variability between the control and intervention branches.

Assess whether there are differences in weight and body composition between the control and intervention branches.

Assess the presence of frailty and whether the condition changes after the intervention.

Assess the presence of obesity and whether this condition changes after the intervention.

Assess the usefulness of using devices (wearables) in the process of self-management of the disease.

Assess the usefulness of using apps based on artificial intelligence in the process of self-management of the disease.

Evaluate improvement in the quality of life of patients and in the internal and external perception of the disease.

METHODS

3.1- Study design

Non-pharmacological, randomized, multicenter pilot study aimed at self-management of DM in people with the disease in an outpatient setting, with a 14-week follow-up.

3.2- Sample size, recruitment and randomization.

Sample size

Based on previous studies [16], a sample size of 198 patients would be sufficient to provide 90% power to detect a 0.7% between-group difference in HbA1c levels, assuming a pooled standard deviation (SD) of 1.6, a two-sided Type I error of 0.05, and a loss rate of 15%.
We used R Core Team (2024). R: A language and Environment for Statistical computing. R Foundation for Statistical computing, Vienna, Austria. https://www.R-project.org. R version 4.4.0.
For sample size we used: Rotondi MA (2018). Epibasix: elementary epidemiological functions for epidemiology and biostatistics. R package version 1.5

Recruitment

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Patients will be recruited in consultations from primary clinics or hospital outpatient clinics of the Extremadura health system (SES) by the study researchers. After being informed, they must meet the inclusion and exclusion criteria and must sign informed consent (Annexes I and II).
Once the consent has been signed, all patients will be administered the following tests to be carried out at home until the first study visit: Diabetes self-management questionnaire revised (DSMQ-R, Annex III), Summary of Diabetes Self-Care Activities (SDSCA, Annex IV), Diabetes stigma Assessment Scale (DSAS-2, Annex V), Diabetes treatment satisfaction (DTS, Annex VI), EuroQol (EQ-5D, Annex VII) and the International physical activity questionnaire (IPAQ, Annex VIII). Likewise, the patient will be provided with a blood sample collection form, with the usual parameters (described in the variables section.)
The patient will then be called (figure 1) for the first study visit, which will be carried out by the patient's monitor. During this first visit, patients must complete the tests and ask questions if they have any. During this first visit, new tests will be performed: Fried (Annex IX), Short Physical Performance Battery (SPPB, Annex X) and Diet Recall Questionnaire (Annex XI). Anthropometric and clinical measurements of the patients will also be taken.
Once the tests have been completed, they will be randomized.

Randomization

At each enrollment session at each center, prior to the enrollment day, the selected and scheduled participants, ordered alphabetically by the first letter of their surname, will be randomly assigned a number. Once the number is assigned, in a second randomization process, half of these numbers will be assigned to the intervention arm and the other half to the control arm. If the number of scheduled patients is odd, more or fewer participants will be assigned to each arm at each enrollment center throughout the period, in order to obtain two arms with a similar number of participants.

All patients will be given lifestyle advice and will undergo continuous glucose monitoring with Abbott FreeStyle Libre 3© devices, along with step and heart rate monitoring using a wrist device (Smartwatch). Those who are going to be randomized to the intervention arm will also be provided with the relevant information for the management of an application that will be

downloaded to their mobile device and that will contain explanatory videos of the physical activity program, nutritional advice and motivational flash cards that will be integrated with an artificial intelligence tool (Kinetikos©).

The first visit will be carried out with groups of several patients who will be scheduled in advance by each of the collaborating researchers. From each of these groups, 50% will be randomly assigned to the control arm and the other 50% to the intervention arm.

The associated researchers will also receive training in the use and reception of information from the devices that will be used.

3.3 Inclusion and exclusion criteria

Inclusion criteria

- Patients over 18 years of age.
- Diagnosis of DM: made according to guidelines [14] and with a baseline glycosylated hemoglobin (at the beginning of the study) above 7.5%
- At least one known vascular risk factor (high blood pressure, dyslipidemia, smoking, obesity or chronic kidney disease) or established vascular disease (coronary disease, cerebrovascular disease or peripheral arterial disease).
- Ability to use a smartphone-type mobile device.
- Having signed informed consent (by patient or representative).
- Score equal to or less than six points on the DSMQ-R questionnaire.

Exclusion criteria

- Patients with DM but without other risk factors or associated established vascular disease.
- Score greater than sis points on the DSMQ-R questionnaire.
- Patients with neurological diseases or tumors in advanced stages, who are unable to adequately carry out a basic physical activity program.
- Patient participating in a clinical trial of pharmacological intervention.

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3.4 Study variables

• **Demographic data:**

- Province: nominal variable.
- Place of habitual residence, by number of inhabitants: less than 2000-between 2000 and 5000-between 5000 and 50,000-between 50,000 and 500,000-more than 500,000 (categorical variable)

• **General data:**

- Patient code: identification code assigned to each patient participating in the registry and assigned by the coordinating team. Nominal variable.
- Order number: This is an internal number for patient identification. A successive number will be assigned to the patients recruited at each centre. Ordinal variable.
- Recruitment: dichotomous nominal variable that includes 2 categories: intervention/control.
- Sex: dichotomous variable that takes Male/Female as values. Date of birth: Patient's date of birth (dd/mm/yyyy).
- Level of education: No studies-primary-secondary-university. Categorical variable.
- Marital status: married-single-widowed-others. (Qualitative, nominal variable)
- Employment status: Working/Unemployed/Retired/Others (Qualitative, nominal variable)
- Residence: Single-family home/Semi-detached house/Apartment/Residential/Assisted residence (Qualitative, nominal variable).
- Family environment: lives alone/with partner/with children/with other people
- Caregiver (yes/no). If yes: partner-first-degree relative-other relative-other person. Categorical variable.

• **Personal history**

- Heart failure: Dichotomous variable (yes/no). If yes, categorical variable: HF with depressed LVEF/HF with intermediate LVEF/HF with preserved LVEF.

- High blood pressure: dichotomous variable (yes/no).
- Years since high blood pressure was diagnosed, (Categorical variable: more or less than 10 years/unknown).
- COPD: dichotomous variable (yes/no).
- Years since COPD was diagnosed, (Dichotomous variable: more or less than 10 years).
- Sleep apnea-hypopnea syndrome (SAHS): diagnosis must be recorded by sleep polygraphy. Dichotomous variable (yes/no).
- Years since SAHS was diagnosed, (Categorical variable: more or less than 10 years/unknown).
- Smoking: Smoker/ex-smoker/non-smoker (categorical variable)
- If smoker, time since smoker started (categorical variable: more or less than 10 years/unknown).
- Dyslipidemia: based on cholesterol levels or history of lipid-lowering treatment. Dichotomous variable (yes/no).
- Established cardiovascular disease: Dichotomous variable (yes/no). If yes, categorical variable: ischemic heart disease/stroke/peripheral artery disease.
- Chronic kidney disease (CKD-EPI estimated glomerular filtration rate < 60 ml/min and/or albumin creatinine ratio > 60 mg/g, at least in the six months prior to inclusion). Dichotomous variable (yes/no).
- Cognitive disorder: dichotomous variable (yes/no).
- Thyroid disease: dichotomous variable (yes/no). If affirmative, Hypo- or Hyperthyroidism.
- Venous thromboembolic disease (yes/no).
- Neoplastic disease with active treatment (dichotomous variable, yes/no), if affirmative, type of neoplasia (nominal variable)

• **Physical examination variables:**

- Weight: Measured in the consultation, with the patient barefoot, recorded in Kilograms. (quantitative variable)
- Height: Measured with a stadiometer, standing, with the patient barefoot and in an upright position. It should be recorded in centimeters. In case the patient's

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condition prevents its measurement, the height can be estimated by the method that the researcher deems appropriate. (quantitative variable)

- SBP (Systolic blood pressure, in mmHg): quantitative variable. Measured in the consultation.
- DBP (Diastolic blood pressure, in mmHg): quantitative variable. Measured in the consultation.
- HR (Heart rate, in beats per minute): quantitative variable, measured in the consultation.
- Waist circumference: measured in centimeters with the person standing, with feet together, arms at the sides and abdomen relaxed. Then, wrap the measuring tape around the abdomen at the height of the navel and, without pressing, take a deep breath and then exhale. (Quantitative variable).
- Hip circumference: taken at the height of the maximum relief of the buttocks, it may coincide with the height of the pubic symphysis. The evaluator stands to the right of the subject being measured, ensuring that the tape remains in the horizontal plane. The subject stands with feet together without contracting the buttocks and arms crossed over the chest. (Quantitative variable, in centimeters)
- Calf circumference: Place the measuring tape horizontally around the calf and move up and down to locate the maximum circumference in a plane perpendicular to the longitudinal axis of the calf. The measuring tape should be in contact with the skin around the entire circumference but should not produce pressure. Measured in centimetres. Quantitative variable.
- Hand dynamometry: measurement of the dominant hand. The test will be taken as the average of the measurements, which will be 10 attempts, the maximum value -all expressed in kilograms- and the coefficient of variation. (Quantitative variables).

• **Scales and tests:**

- To be completed by the patient at home: Diabetes self-management questionnaire revised (DSMQ-R, Appendix III), Summary of Diabetes Self-Care Activities (SDSCA, Appendix IV), Diabetes stigma Assessment Scale (DSAS-2,

Appendix V), Diabetes treatment satisfaction (DTS, Appendix VI), EuroQol (EQ-5D, Appendix VI) and the International physical activity questionnaire (IPAQ, Appendix VII). Discrete/categorical quantitative variable.

- To be performed in the consultation by the study monitor: Fried Frailty Scale (Annex VIII), Short Physical Performance Battery (SPPB, Annex X) and Charlson comorbidity (Annex XI).

• **Body composition:** Body composition will be obtained in the consultation from bioimpedance measurement. Measurements will be obtained regarding fat mass content, skeletal muscle mass and if possible skeletal appendicular muscle mass and water content.

• **Analytical parameters (Quantitative variables)**

- According to standard techniques of the hospital laboratory, the following parameters will be determined in blood: Total leukocytes (10^9/L), Total neutrophils (10^9/L), Total lymphocytes (10^9/L), Hemoglobin (g/dl), Hematocrit (%), Total platelets (10^9/L), MPV (mean platelet volume, fL), Glucose (mg/dl), Glycosylated hemoglobin (HbA1c, %), Creatinine (mg/dl), Urea (mg/dl), Sodium (mEq/L), Potassium (mEq/L), Total cholesterol (mg/dL), HDL and LDL cholesterol (mg/dL), Triglycerides (mg/dL), Albumin (g/dl), GOT-AST (IU/L), GPT-ALT (IU/L), GGT (IU/L), Urate (mg/dL), C-reactive protein (mg/dL), Ferritin (mg/dL), Transferrin (mg/dL), Calcium (mg/dL), Phosphorus (mg/dL), vitamin D.
- In urine: albumin-creatinine ratio (mg/g creatinine), provided that urinary tract infection is ruled out).

• **Basal treatment:**

- ACEI/ARA2/ARNI Which one?
- Loop diuretic Which one?
- Thiazide Which one?
- Statin Which one?
- Ezetimibe

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- Other lipid-lowering drugs
- Antiplatelet agent Which one/ones?
- Anticoagulant Which one?
- Non-insulin antidiabetic agent:
    - DPP4 inhibitor Which one?
    - SGLT-2 inhibitor Which one?
    - Partial agonist of the GLP-1 receptor Which?
    - Sulfonylurea Which?
    - Biguanide Which?
    - Thiazolidinedione Which?
- Insulin:
    - Rapid: if yes, number of units/day.
    - Basal: if yes, number of units/day.
    - Mixture: if yes, number of units/day.
- Calcium antagonist Which?
- Beta-blocker Which?
- Antidepressants Which?
- Benzodiazepines Which?
- Total number of medications per day (quantitative variable).

• **Follow-up variables** (7 weeks in the case of the intervention arm, 14 weeks -final visit- of the pilot project):

- The intervention arm will have a follow-up visit 7 weeks after the start of the pilot. This is a booster visit with your doctor/nurse in charge (associate researcher), and no variables will be collected, unless there is an adverse event that has not been previously collected. If this is not the case, the date of the review will simply be collected (date variable) and whether or not the patient attends (dichotomous variable)
- Parameters derived from wearables:

- Continuous glucose monitoring: The times in the glycemic range, time (%) in hyper and hypoglycemic ranges and glycemic variability will be obtained. (Quantitative variables)
- Smartwatch: Number of steps, daily time of physical activity, average calorie consumption derived from physical activity, heart rate. (Quantitative variables)
- Kinetikos (artificial intelligence app): parameters derived from the patient's physical activity (% time of arm and leg movement, quality of exercise, risk of falls). Quantitative variables.

- Death (yes/no): dichotomous variable
- Date of death. Date variable
- Cause of death. (categorical variable: cardiovascular/HF/infection/hemorrhagic complication/Other)
- Adverse event. (yes/no, dichotomous variable)
- Date of adverse event. Date variable
- Type of adverse event. (nominal variable): since the pilot project is not a pharmacological intervention, adverse events will be considered those that cause the planned physical activity to not be carried out, such as accidental falls or other processes (related to health or not) that interfere with the proper follow-up of the program. These events will be recorded nominally. Hospitalizations and visits to the emergency room are excluded and are coded separately. Likewise, any adverse pharmacological reaction will be coded separately, even if it does not affect the follow-up of the program. Adverse drug effect (yes/no, dichotomous variable)
- Date of adverse drug effect. Date variable
- Type of adverse drug effect: brief description of the same (Nominal variable)
- Hospitalization (yes/no, dichotomous variable)
- Date of hospitalization (date variable)
- Cause of hospitalization. (nominal variable)
- Number of emergency room visits (quantitative variable).
- Changes in baseline treatment (yes/no, dichotomous variable)
- Description of the treatment changes (nominal variable)

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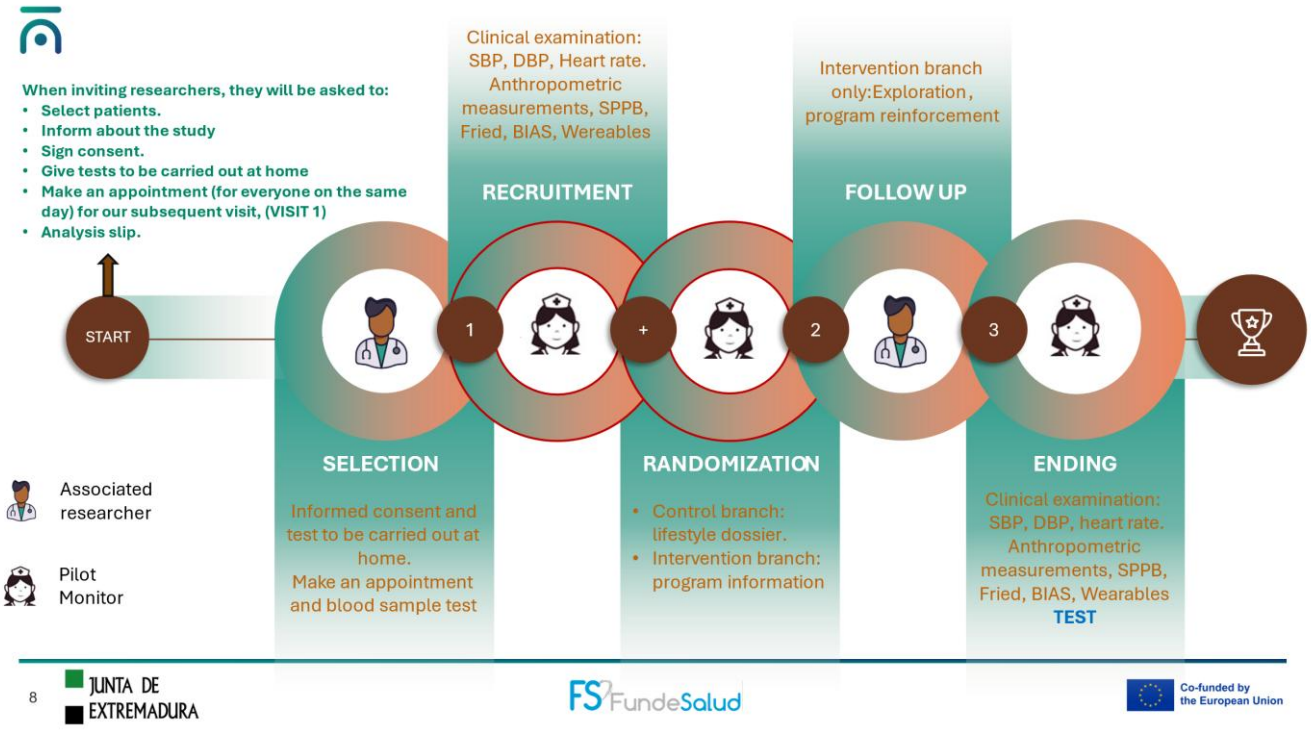
- Analytical variables (at the end visit): Total leukocytes (10^9/L), Total neutrophils (10^9/L), Total lymphocytes (10^9/L), Hemoglobin (g/dl), Hematocrit (%), Total platelets (10^9/L), MPV (mean platelet volume, fL), Glucose (mg/dl), HbA1c (%), Creatinine (mg/dl), Urea (mg/dL), Sodium (mEq/L), Potassium (mEq/L), Total cholesterol (mg/dL), HDL and LDL cholesterol (mg/dL), Triglycerides (mg/dL), Albumin (g/dl), GOT-AST (IU/L), GPT-ALT (IU/L), GGT (IU/L), Urate (mg/dL), C-reactive protein (mg/dL), Ferritin (mg/dL), Transferrin (mg/dL), Calcium (mg/dL), Phosphorus (mg/dL), vitamin D. In urine: albumin-creatinine ratio (mg/g creat), provided that urinary tract infection is ruled out).
- At the final visit, the tests from the initial visit will be repeated: Diabetes self-management questionnaire revised (DSMQ-R, Appendix III), Summary of Diabetes Self-Care Activities (SDSCA, Appendix IV), Diabetes stigma Assessment Scale (DSAS-2, Appendix V), Diabetes treatment satisfaction (DTS), EuroQol (EQ-5D, Appendix VI) and the International physical activity questionnaire (IPAQ, Appendix VII). Discrete/categorical quantitative variable. Fried frailty scale (Appendix VIII), Short Physical performance Battery (SPPB, Appendix X). The Charlson comorbidity scale (Appendix XI) will not be used.

Anthropometric measurements from the initial visit will also be performed again, along with weight and body composition by bioimpedance.

The development of the program is displayed in the following figure (figure 1):



3.4 Statistical analysis

A descriptive statistical analysis of the variables collected in the pilot will be performed, presenting the absolute and relative frequencies of the qualitative variables, as well as the measures of central tendency and dispersion of the quantitative variables (mean, standard deviation, median, minimum and maximum). The 95% confidence intervals will be presented for the main quantitative outcome variables associated with the main objective and the main secondary variables.

Depending on the analysis carried out and provided that the variable contains at least 75% of the records correctly completed, data imputation can be performed using a validated methodology for this purpose (KNN, K-nearest neighbour preferably if the variable is quantitative).

In the inferential analysis, parametric tests will be used for those continuous variables that meet the application conditions (e.g. t-test) and non-parametric tests (e.g. Kruskal-Wallis, U Mann Whitney, etc.) for variables that do not meet parametric criteria. In the case of qualitative or categorical variables, the Chi-square test will be used or, where appropriate, the Fisher exact test. Multivariate regression analyses will also be performed when necessary. The

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models will be created a priori with variables that have statistical significance in the univariate analysis or that are considered relevant based on previous experience.
The hypothesis tests performed will be bilateral in all cases and with a significance level of 0.05.

3.5 Data Collection

The data will be collected using a case report form (CRF) in electronic format (CRFe), which will depend on the sponsor of the study (JACARDI, EU4Health programme of the European Union) and which will be included in the environment associated with RedCap, which will be supervised by a monitor. In this regard and in relation to access to the data:

- Users will only have access to those resources that they need for the development of the pilot programme (each patient will have individualised information from the wearables).
- The registry monitor will ensure that there is an updated list of users and user profiles, and the authorised access for each of them.
- The registry monitor will establish mechanisms to prevent a user from accessing resources with rights other than those authorised.
- Only authorized personnel, a list that is available to all participants in the different phases of data processing, may grant, alter or cancel authorized access to the resources, in accordance with the criteria established by the registry monitor (Access types: administrator, user, reading, reading and writing).
- In the event that there is personnel outside the registry monitor who has access to the resources, they must be subject to the same security conditions and obligations as the registry's own personnel.

TASKS AND RESPONSABILITIES

4.1 Responsibilities of the scientific-technical committee

The scientific-technical committee of the pilot project will be responsible for providing scientific advice and recommendations regarding:

The protocol and the data collection notebook.
The methodology.

The data analysis plan.

4.2 Responsabilities of associated researchers

The selection of patients and the follow-up of those included in the intervention arm will be carried out by the research associates in accordance with this protocol and the legal provisions in force in the country.

It is the responsibility of the research associate to obtain informed consent from the patients in writing before their inclusion in the study.

The research associate, or the person designated by the research associate for this purpose and under the responsibility of the research associate, will be responsible for providing the patient with the pilot project information sheet concerning all aspects of the study, including written information.

Before a patient is included in the study, the patient will sign the informed consent document, indicating his or her name and dating the document personally (alternatively this may be done by the patient's legal representative), as will the person obtaining the consent. A copy of the signed and dated informed consent document will be given to the patient, while the original copy will be kept by the research associate.

Finally, the associate researcher will be responsible for administering the tests to be carried out by the selected individual at home, providing the analytical form with the parameters indicated in this protocol and generating appointments for subsequent visits (recruitment, randomization, follow-up and completion), in accordance with the project monitor.

4.3 Responsabilities of Pilot monitor

The project monitor will be in charge of carrying out the recruitment and randomization visits, as well as the final visit of the project. He/she will be in charge of carrying out the tests and scales provided for in this protocol.

Likewise, the project monitor will be in charge of providing the patient with all the information concerning all aspects of the project that may have arisen after reading it and similarly any doubts that may have arisen after carrying out the tests that were carried out at home.

The registry monitor will ensure that there is an updated list of users and user profiles, and the authorized access for each of them.

Finally, the monitor will be in charge of completing the CRFe and collecting all the data relating to the research. The researcher must guarantee the precision and veracity of the data recorded in the CRFe.

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4.4 Responsabilities of sponsor

The sponsor of the study (JACARDI, EU4Health programme of the European Union) will be responsible for taking all reasonable measures and providing sufficient resources to ensure the proper conduct of the study. It will also be responsible for appointing a monitor responsible for the proper functioning of the registry.

ETHICAL ASPECTS

Patients included in this project will be treated with medical care following standard clinical practice in accordance with the guidelines of each centre. The study will be carried out in accordance with the Declaration of Helsinki.

Approval from the Clinical Research Ethics Committee (CEIC) of the ¿? Hospital will be requested prior to beginning registration.

The associated researchers of each participating centre will explain to each patient all aspects of the registry and will be given an information sheet giving details of this, making it clear that participation is voluntary and that they can leave the registry at any time if they wish. If the patient wants to participate, both the researcher and the patient themselves, or their legal representative in case of incapacity, must sign the informed consent as explained in the previous section.

The monitors participating in the registry undertake that all clinical data collected from the study subjects will be separated from personally identifiable data to ensure patient anonymity in compliance with current guidelines on Personal Data Protection, Regulation (EU) 2016/679 of the European Parliament and of the Council of 27 April 2016 on General Data Protection (GDPR) and Organic Law 3/2018 of 5 December on the Protection of Personal Data and the Guarantee of Digital Rights, as well as any other applicable sectoral regulations.

5.1 Confidentiality Agreement.

All unpublished material, information (oral or written) and documentation provided to the investigators and monitors, including this protocol and the CRDe, are the exclusive property of the sponsor.

Neither the investigator, monitor nor any person on their team may transfer or disclose such materials or information (either in whole or in part) to any unauthorized person, without first obtaining the formal written consent of the sponsor.

Both the investigator and the monitor will consider all information they receive, acquire or deduce during the study to be confidential and will take all necessary measures to ensure that confidentiality is not breached except in cases where information must be transmitted by legal imperative.

5.2 Documents conservation.

The monitor must organize the conservation of the study documentation until the end of the study, respecting for these purposes, also, all the regulations and specific recommendations concerning the conservation of clinical records.

FINANCIAL INFORMATION

This pilot project does not include any payments for either the associated researchers or the participating patients. It also does not include any non-routine laboratory tests.
Each participating patient will be provided with continuous glucose monitoring devices corresponding to the duration of the pilot project, at the expense of the sponsor (JACARDI).
Each participant will also be given a smartwatch device for monitoring health data during the programme, also at the expense of the project sponsor. The intervention branch will also be given the “Kinetikos” app with access to it from the mobile device. The licenses for its use for one year will also be at the expense of the funds provided by the sponsor.
Finally, funds are also provided for the contracting of insurance and the pilot project monitor. A detailed table is attached in Annex XII.

PROCEDURES

7.1 Visits schedule

After patient selection by the associated researchers, patients will be given a first recruitment and randomization visit as previously described. Subsequently, only the intervention arm will be given an in-person visit seven weeks after inclusion, and finally all patients will have a final in-person visit 14 weeks after inclusion.

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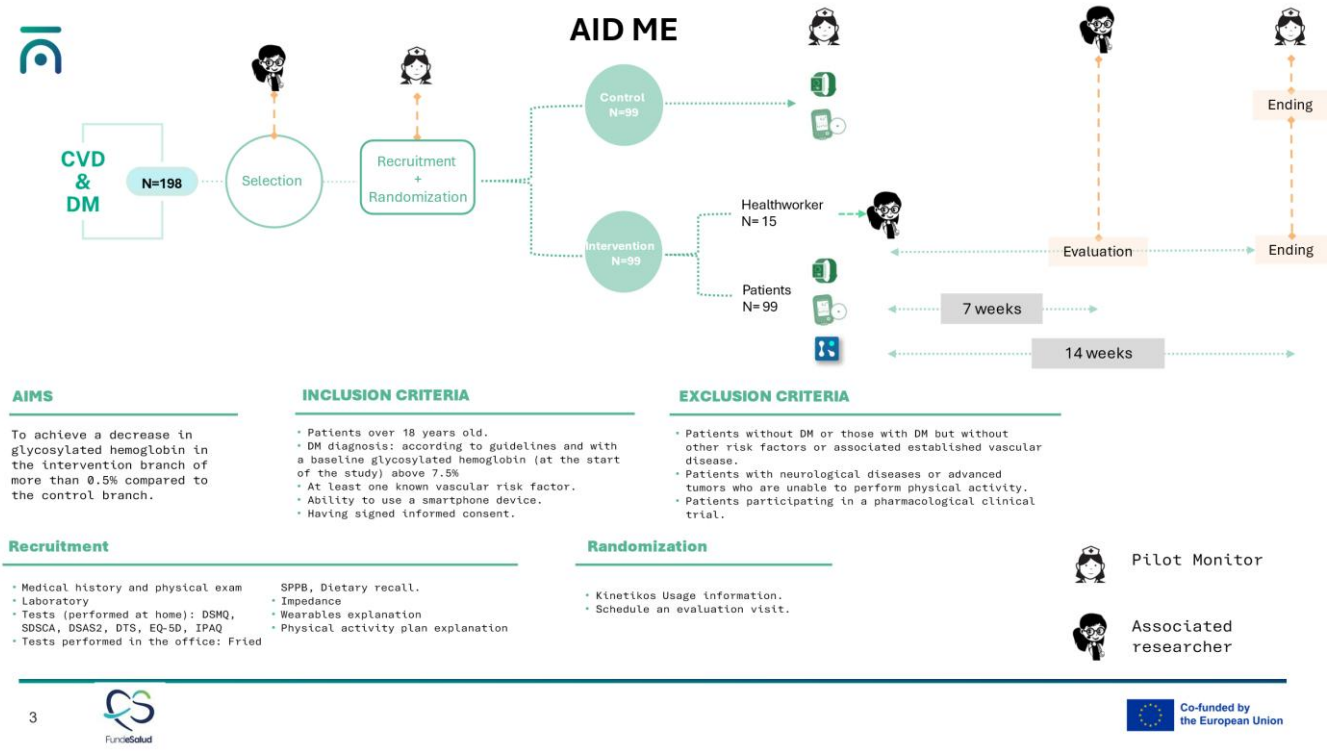
7.2 Timeline.

The program is scheduled to begin enrolling patients in February 2025. The enrollment period may remain open for the following months until October 2025, and will close once the planned sample size has been reached. The program will close 14 weeks after the last patient has been enrolled.

The study procedures are outlined in the following figure (figure 2).



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ANNEXES

9.1 Annexe I: Informed consent

INFORMED CONSENT – INFORMATION FOR PATIENTS
Before proceeding to authorize and sign this informed consent, please read the information provided below carefully and ask any questions you may have.

Project title:
JACARDI-122 PILOT PROJECT
Aid for the Comprehensive Self-Management of Type 2 Diabetes Mellitus (AID ME)
Principal Investigator:
Dr. José Carlos Arévalo Lorido
FUNDESALUD
Email: jose.arevalo@salud-juntaex.es
Sponsor: FundeSalud - Extremadura Health Service (SES) - Regional Government of Extremadura. This promoter is supported by the JACARDI project, which received funding from the European Union (EU4HEALTH) through the Joint action on cardiovascular diseases and diabetes, JACARDI.
Nature:
This document is an informed consent to participate in a pilot study that will evaluate the effectiveness of joining a program to help you manage your diabetes mellitus, in terms of improving your glycemic control (control of your glucose or blood sugar), as well as your progress in self-knowledge of lifestyles (physical activity and diet) that help you better manage your day-to-day life with the disease. The results we obtain from your participation will help us to assess the usefulness of this program and, if this is positive in your case, to be able to implement it in our health system and thus be able to help more people who, like you, live with diabetes mellitus.
The tests that are going to be carried out on you are not in any way invasive, nor are they intended to be detrimental to your health. You will be given some questionnaires that have to do with your current management of diabetes mellitus, as well as your quality of life and some aspects related to your day-to-day life in your environment and that will be treated anonymously. Furthermore, your medical treatment is not intended to be modified, and if it is

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necessary to do so, it will be in accordance with standard clinical practice and no action will be taken outside of clinical practice guidelines or any “experimental” treatment will be used.
What we intend with this project is to provide you with tools that will help you to better manage your day-to-day life with diabetes mellitus. In this way, you will be provided with various devices that will accompany you during the program and that you will have to learn to use: if you do not use it already, you will have a continuous glucose sensor (transdermal patch to check your blood glucose at all times through your mobile device). In addition, you will be provided with a smart watch to collect activity data during the project and you will be provided with a program where you can access advice on your diet and various exercises adjusted to your initial physical situation aimed at improving your activity and therefore improving your physical condition. The project consists of two branches (two groups) to which you will be accessed randomly. The difference between one branch or group or another is the way of accessing these exercises and advice (in one in paper format, in another in digital format) and in the follow-up of them, with more information for you and your doctor in one branch, and a closer follow-up of said activity in that same branch.
The duration of the program will be 14 weeks (approximately three months).
The only thing we require from you is that you have and know how to use a mobile device (mobile phone) or a smart phone.
Read this document carefully and ask all the questions you consider appropriate to the researcher who is proposing your participation. If you need additional information or any clarification later, you can contact the email addresses and/or telephone numbers indicated. If you decide to participate in this project, you must give us your consent.

Type of study:

The study in which we are inviting you to participate is a study called a pilot project, which means that with the results we obtain from your participation we will be able to better assess the usefulness of the program. You do not have to take any treatment other than what your doctor thinks is necessary to treat you, nor undergo any special diagnostic tests. We researchers simply limit ourselves to finding out what happens during the duration of the project, which, as we have informed you, is 14 weeks.

Implications for the patient:

If you decide to participate in the study, you will only have to collaborate in carrying out the surveys, answering the questions that the researcher will ask you, either to you or to your relatives or representative (in case you are unable to do so) and you will also have to collaborate in learning and carrying out the programmed physical activity together with the use of the devices that we provide you. Some data from your clinical history necessary to make an adequate assessment of the situation of your disease will also be recorded.
Both the project monitors and the professionals who care for you undertake that the results of the project will be used exclusively for health purposes, for your better care and for this scientific research.

Therefore:

• Participation in the study is completely voluntary.
• You may request that your data be withdrawn from the study when you so indicate, without giving explanations and without this affecting your necessary medical care.
• All personal data obtained in this study are confidential and will be treated in accordance with the Organic Law on Personal Data Protection 15/99.
• The information obtained in the project will be used exclusively for the specific purposes of the project.

9.2 Annexe II: Informed consent form for participants in the AID ME project

PATIENT CONSENT FORM FOR THE USE OF THEIR CLINICAL AND FOLLOW-UP DATA IN THE PILOT PROJECT: Aid for the Comprehensive Self-Management of Type 2 Diabetes Mellitus (AID ME)

Dear ……...,
As we have already explained to you, our pilot project Aid for the Comprehensive Self-Management of Type 2 Diabetes Mellitus (AID ME) aims to offer you the best healthcare.
As already mentioned in the information sheet, we intend to collect data from your medical history, physical examination and analysis related to your diabetes mellitus, and provide you with a program to help you improve your day-to-day life with diabetes by paying attention to lifestyle modifications (diet and physical activity).
Our experience so far has been very satisfactory and in order for us to advance and improve every day it is very important that we can evaluate and measure this activity that we develop. That is why we need to use the data provided by the participants, and in this way objectively know all the aspects related to the care that we provide. Likewise, our experience can also be useful for other doctors and other people who live with diabetes mellitus, so we also want to be able to publish it in medical journals. Therefore, we require your authorization to be able to collect the information derived from our project anonymously.
Information regarding the processing of personal data.
We inform you that your personal data and/or biological samples will be processed in strict compliance with Law 14/2007 of July 3, on Biomedical Research, as well as with Regulation (EU) 2016/679, of the European Parliament and of the Council, of April 27, 2016, General Data Protection Regulation and Organic Law 3/2018, of December 5, on the Protection of Personal Data and Guarantee of Digital Rights:

Data controller.
You can contact us through:
FundeSalud - Servicio Extremeño de Salud (SES) - Junta de Extremadura.
Grupo Investigador Multidisciplinar Extremeño – GRIMEX (FundeSalud).
C. Sierra Nevada, 10, 06700 Villanueva de la Serena, Badajoz
-Telephone: 924847838
-Email: jose.arevalo@salud-juntaex.es

Purposes of data processing.
The data will be processed for the purpose of managing your participation in the AID ME pilot project, as well as incorporating your biometric or health-related data into it.
Likewise, the data provided and collected will be used for:
- Management of participation in the clinical study, monitoring of the study, carrying out checks, monitoring and tests in relation to the clinical study.
- Preparation of results and publication of results. The data collected for the study will be identified by a code, so that no information that could identify you is included.
- In addition, for the correct implementation of the AID ME pilot project, data processing of the relevant clinical documentation of the patients included in the registry will be carried out under the supervision of the researchers and for the sole purpose of checking compliance with the protocol, ensuring that the data are recorded correctly and completely.

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- Where appropriate, the data provided in this AID ME pilot project may be used for studies/research that are carried out subsequently, in which case coding systems will be applied to these data, after pseudonymisation of the data.

Legitimacy of data processing.
The basis that allows us to process your data is the express written consent that you give for your participation in the AID ME pilot project.
You also give your consent for the data collected and obtained from this study/research to be processed, with the same guarantees of pseudonymisation, for other studies/research that may be carried out by the controller. In these cases, you will be informed in advance of the purposes of this new study/research.
We inform you that you can revoke this express consent at any time. In the event of revocation, the data provided and collected cannot be deleted, in order to guarantee the validity of the research and comply with legal obligations.

Storage periods.
The data will be kept until the purpose of the study is considered to have been fulfilled, and will be deleted when the legally established periods of Law 14/2007 of July 3, on Biomedical Research, expire, with the exceptions provided for in the section “Rights of the interested party”.
These periods do not affect your clinical history, which is owned by the Health Center/Hospital, and whose conservation is subject to the periods established in Law 41/2002, of November 14, regulating basic patient autonomy and rights and obligations regarding information and clinical documentation.

Security measures and pseudonymization of data.
The research team will process your data by taking the appropriate measures to protect it, subjecting it to encryption, so that your identity is preserved.
Your identifying data, such as your name and surname, ID, health card, social security number, address and telephone number will not be included in the trial, and will only be known by the Principal Investigator, as well as by the personnel authorized for this purpose, to guarantee your safety and monitor your health status.
In addition, the results of the research carried out will be completely anonymous.

Communications to third parties and international transfers.
Your data will not be transferred to third parties, except in those cases expressly provided for by law.
However, the information and results may be communicated, after pseudonymizing the data, to your collaborators in accordance with their strict need to know them for the performance of the study/research.
In the event of an international transfer of pseudonymized data for the purposes of the research and/or for the storage of information, appropriate security measures will be adopted in accordance with the provisions of European data protection regulations.

Rights of the interested party.
At any time, you may exercise your rights of access, rectification, deletion, opposition, limitation of processing and portability of data, as well as withdraw the consent previously

given, if applicable, by sending a written communication, with a copy of your valid ID, to the contact addresses indicated above.
Participation in the trial is voluntary, and the revocation of consent will not entail the destruction of the data already provided, so as not to distort the results of the research, although no new data will be collected.
In addition, any results of the research carried out will be anonymous. If it is necessary to publish results that include personal data, we will request your express consent.
You may also file a claim with the Spanish Data Protection Agency, if you consider that your rights have not been adequately addressed.

1. Consents

Consent by representation. When the participant is not legally emancipated, is under 16 years of age or has had his or her legal capacity judicially modified, according to article 4 of Law 14/2007, of July 3, on Biomedical Research, he or she may give consent through his or her legal representative or through representation of both parents or only one of the parents, with the tacit and documented consent of the other.
However, he or she will participate to the extent possible and according to his or her age and capacities in decision-making throughout the research process.
When he or she reaches or recovers the capacity to consent by himself or herself, his or her consent must be obtained to continue participating in the project.
I have been informed of the purposes of the study/research, I understand and give my express consent to FundeSalud/Junta de Extremadura to participate in this research project.

Signature and name and ID of the participant over 18 or of his or her legal representative

In _____ on _____ of _____ of 20_

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REVOCATION

Mr./Mrs._____ of _____ years of age, with address at _____
_____and D.N.I. No. _____,

As participant/legal representative of Mr._____, with DNI No._____
I REVOKE the consent given on _____ and do not wish to continue participating in the **AID ME** pilot project.

The revocation of the consent given that I request will not entail the elimination of the data already provided to the study/research in which I have participated in order to guarantee the validity of the research and to comply with legal obligations.

In _____ on _____ of _____ of 20_

9.3 Annexe III: Diabetes self-management questionnaire revised (Spanish version)

9.4 Annexe IV: Summary of diabetes self-care activities measure (SDSCA, Spanish version)

9.5 Annexe V: Diabetes stigma assessment (DSAS-2, Spanish version)

9.6 Annexe VI : Diabates treatment satisfaction questionnaire (DTSQ, Spanish version)

9.7 Annexe VII : Quality of life (EQ-5D, Spanish version)

9.8 Annexe VIII: International physical activity questionnaire (IPAQ, Spanish version)

9.9 Annexe IX : Fried phenotype frailty scale (Spanish version)

9.10 Annexe X: Short physical performance battery (SPPB, Spanish version)

9.11 Annexe XI: Dietary recall 24 hours (Spanish version)

9.12 Annexe XII: Financial resume

9.13 Annexe XIII: CEIM approval

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