Feasibility and Effectiveness Study through a Randomized Clinical Trial of an Intervention Based on Sending SMS Text Messages to Promote Adherence to Antidiabetic Medication and Healthy Lifestyles in Patients with Type 2 Diabetes Mellitus.

Ignacio Ricci Cabello (Principal Investigator), Rocío Zamanillo.

August 13, 2020.

Summary Background: Type 2 diabetes mellitus (T2DM) is a disease affecting approximately 4 million people in Spain, generating an annual cost of 8 billion €. Recent studies suggest that the use of short text messages (e.g., SMS) sent at scale and at low cost via digital health systems could be an effective strategy to promote adequate self-management and slow the progression of this disease. In Spain, this type of intervention remains under-studied.

The research team previously conducted a qualitative study with patients, clinicians, and psychologists to create short messages that are relevant and acceptable to patients (IB 3948/19 PI from July 31, 2019) and a retrospective cohort study using computerized medical records to identify factors associated with non-adherence, thus developing messages targeted at these factors (IB 3949/19 PI from October 30, 2019). We are currently conducting a pre-pilot study to finalize adapting the available health information system to send text messages to the mobile phones of 40 patients with T2DM (IB 4105/20 PI from May 20, 2020).

Objective: To pilot and evaluate an intervention based on the use of a mobile technology system integrated with computerized medical records to send personalized short text messages to mobile devices to promote adherence to antidiabetic medication and healthy lifestyles in patients with T2DM.

Methods: A feasibility study followed by an evaluation study of the intervention's effectiveness through a randomized clinical trial with parallel groups involving 200 patients and 3 months of follow-up (feasibility study) and 740 patients and 12 months of follow-up (effectiveness study).

This work will assess the intervention's impact compared to a control group receiving usual treatment (control group) on blood glucose levels (primary outcome variable), lifestyle changes (physical activity and diet), and adherence to antidiabetic medication.

Relevance and Expected Impact: This study will determine whether it is feasible and effective to offer a personalized mobile messaging service based on clinical health outcomes of patients with type 2 diabetes to improve disease self-management and translate into better blood glucose levels, therapeutic treatment adherence, and adoption of a healthy lifestyle such as the Mediterranean diet and physical activity.

Introduction, Background, and Current State of the Issue Type 2 diabetes is a chronic disease that affects 4 million people in Spain. The treatment includes antidiabetic medication and lifestyle changes to prevent associated complications (cardiovascular

disease, retinopathy, neuropathy, and nephropathy, among others). Adherence to antidiabetic medication is significantly low: according to previous studies in Spain, it ranges around 45-52%. Improving adherence to antidiabetic medication therefore represents a significant challenge for our Health System. Likewise, adherence to healthy lifestyles is also a current public health challenge in Spain.

Interventions aimed at improving medication adherence evaluated to date have not proven highly effective, as with adherence to healthy lifestyles, highlighting the need for new approaches to improve both aspects. Interventions based on messaging services (SMS, Short Message Service), commonly referred to as mHealth interventions, have sparked notable scientific interest due to their potential effectiveness, low cost, and high scalability. However, further studies are needed to determine their effectiveness. Considering that Spain is among the countries with the highest mobile phone usage ratio globally (95% of users aged 16-74), and no trials on the subject have been identified in Spain, it becomes necessary to assess the effectiveness of such an intervention to improve diabetes self-management and reduce its complications.

Below, the protocol for two sub-studies encompassed within the DIABETEXT project is detailed: the pilot study and the clinical trial. Given their methodological similarities (virtually identical, except for the number of participants and follow-up duration), we request joint evaluation by the CEI.

Hypotheses FEASIBILITY STUDY:

1. It is feasible to pilot an intervention based on sending personalized text messages according to medical history to promote adherence to antidiabetic medication and healthy lifestyles in type 2 diabetes patients.
2. The intervention is accepted by type 2 diabetes patients.
3. The proposed intervention is useful for type 2 diabetes patients.
4. It is feasible to collect variables before and after the intervention.

EFFECTIVENESS STUDY:

1. An intervention based on sending personalized text messages according to medical history to promote adherence to antidiabetic medication and healthy lifestyles in type 2 diabetes patients reduces glycated hemoglobin (HbA1c) by at least 4 mmol/mol (0.4%) in the intervention group compared to the control group receiving usual treatment during 12 months of follow-up.

Objectives FEASIBILITY STUDY:

1. To evaluate the feasibility of collecting primary and secondary outcome variables for the main clinical trial through a parallel two-arm randomized trial lasting 6 months.
2. To assess acceptance among type 2 diabetes patients to participate in the study and the follow-up rate.

3. To refine the messaging system based on information collected during the 6-month pilot study.

EFFECTIVENESS STUDY:

1. To assess the effectiveness of an SMS-based intervention to promote adherence to antidiabetic medication and healthy lifestyles in patients with type 2 diabetes mellitus.

Materials and Methods This study is preceded by the development and pre-pilot testing of the tool developed in various prior phases, approved by the Balearic Islands Research Committee on the following dates:

1. IB 3948/19 PI: Qualitative study with focus groups to inform the design of an SMS-based intervention to promote adherence to antidiabetic medication in type 2 diabetes patients. July 31, 2019.
2. IB 3949/19 PI: Adherence to oral antidiabetics during the first year of treatment in people with type 2 diabetes treated in primary care centers in the Balearic Islands: A retrospective study based on primary care electronic health records. October 30, 2019.
3. IB 4105/20 PI: Pilot study for the design and evaluation of an SMS-based intervention to promote adherence to antidiabetic medication in patients. May 20, 2020.

Further details on study methodology and intervention design will follow.

Study Population and Recruitment For the feasibility study, the study population will consist of 200 participants (100 per group), all patients from the healthcare service of the Balearic Islands who meet the inclusion criteria. Recruitment will involve identifying eligible patients through a query system developed in the IB 4105/20 PI study. Patients will be contacted via telephone to invite participation and confirm eligibility.

Inclusion Criteria:

- Patients with type 2 diabetes followed by the primary healthcare service of the Balearic Islands.
- At least one active prescription for non-insulin antidiabetics.
- Medication adherence rate below 80% over the last three months.
- Adults aged 18 years and older.
- Mobile phone capable of receiving SMS.
- Ability to read and understand Spanish.
- Recent HbA1c results (>8%) within the last 6 months.

Exclusion Criteria:

- Patients with active insulin prescriptions.
- Conditions complicating participation.

Randomization and Data Collection: Participants will be randomized into intervention and control groups using a validated online system. Intervention participants will receive personalized SMS in addition to usual care. Baseline and follow-up variables, including HbA1c, medication adherence, and technology acceptance, will be collected. Missing data will be managed by contacting clinicians for completion.

For the effectiveness study, the population size increases to 740 participants with similar inclusion criteria and a 12-month follow-up duration.

Expected Outcomes The primary outcome is the change in HbA1c levels. Secondary outcomes include adherence to antidiabetic medication, physical activity, dietary habits, and participant satisfaction. These measures will provide insights into the feasibility and effectiveness of the intervention to promote better management of type 2 diabetes through digital health tools.

Intervention Features

The SMS Sending System Integrated with Health Records: An integrated and semi-automated system has been developed that combines various databases to generate a final file ready to be uploaded to the IBSALUT text messaging platform via the BITSMS portal. In summary, we start with a base of 860 SMS texts about diabetes, prevention of complications, medication, diet, and exercise. Some of these messages are personalized (Annex 2), meaning they are sent only if the participant meets specific criteria, such as elevated blood glucose levels in their latest lab results or obesity (BMI > 30). To achieve this, we developed a system for biweekly queries on the SOPHIA platform in previous phases to program the personalized SMS messages.

Variables not available in health records, such as adherence to the Mediterranean diet (PREDIMED questionnaire), physical activity (IPAQ), mobile internet access, Ramadan practices, and preferred message receipt time, will be collected during the baseline interview with participants.

Message Sending Strategy: Patient profiles will be designed based on adherence to the Mediterranean diet, physical activity levels, and adherence to antidiabetic medication (if the calculation system ultimately allows). A different strategy will be proposed for each profile regarding the

Treatment of Participants' Health Data The files generated from the biweekly queries conducted during the study on the SOPHIA platform, which contain sensitive information as they involve participants' health data, will be stored in a restricted-access folder protected by passwords. Access to this folder will only be granted to technicians from Álamo Consulting, the Information Technology Service of the Balearic Islands

Health Service, and the project's research technicians. Access will require a username and password. The files will be deleted upon completion of the study.

As of August 20, 2020, we received a favorable report from the Data Protection Service of the Balearic Islands Health Service regarding the pilot feasibility study for the design and evaluation of an SMS-based intervention to promote adherence to antidiabetic medication in patients (DIABE-TEXT) (IB 4105/20 PI) (Report attached in supplementary materials). In line with the received recommendations, we include information on the handling of personal data obtained during the DIABE-TEXT study, as well as data included in the Clinical History, in the participant information sheet, and we request express consent for such processing.

Additionally, telephone recordings will be kept as evidence of participants' responses concerning the consent status. If a participant expresses interest in receiving messages on their caregiver's mobile phone, such action will be permitted provided the caregiver authorizes it during the consent recording.

Lastly, the handling of patient identification in the header of SMS messages will be legitimized by the consent provided by the participant regarding their involvement in the DIABE-TEXT study. Such identification will only include the participant's name without disclosing any additional information.

Limitations of the Study The clinical trial could face limitations if an insufficient number of participants are recruited or if there is a high dropout rate during follow-up. Additionally, the use of outcome variables based on information available in clinical records could pose a limitation if there is underreporting of such information. All these aspects will be examined in the proposed feasibility study to address potential problems for the subsequent clinical trial.

Ethical Considerations The proposed study adheres to the principles outlined in the Declaration of Helsinki and complies with good clinical practice standards. The following elements have been considered:

● Participant Information Sheet and Informed Consent Form: Before participants are included in the study, they will receive a Participant Information Sheet (attached) via email. Once they have read it and, if necessary, discussed it with the Principal Investigator, their Informed Consent (attached) will be requested via telephone recording.

● Voluntary Participation: Participants will be informed that their participation is voluntary and that they may withdraw from the study at any time without providing explanations and without any prejudice from their health centers, the Primary Care Management, or the Servei de Salut.

● Confidentiality: The Principal Investigator and the research support technician hired for this project will be the only individuals with access to the registry of study participants.

- Focus Groups (qualitative study): Although discussions will be recorded in audio and video files, participants will be asked not to state their names during

recording. The audio will later be transcribed, and these transcriptions will serve as the basis for analyses. Transcriptions will be anonymized, ensuring that contributors cannot be identified. Videos will be used to identify participants by sociodemographic variables such as gender and age. Additionally, the material may be helpful in cases where audio quality is insufficient for transcription. Only the Principal Investigator and the hired technician will have access to the audio and video and may identify participants if necessary.

- Periodic Queries to Health Records: To personalize message content to participants' clinical characteristics, researchers will need access to specific data from participants' electronic health records. This information will be obtained through the PRISIB platform of the Illes Balears Health Research Institute. The information will be stored in an encrypted file accessible only to the Principal Investigator and the rest of the research team. Participants interested in the study will be informed and must explicitly consent to this access. The database will be permanently destroyed once the message delivery period concludes. Participants cannot be identified using information available in the database generated by the PRISIB platform. Codes required to identify participants will be stored in a separate, independent encrypted database accessible only to the Principal Investigator and the PRISIB platform technician.

● Risks and Benefits: Participation in the study will not provide direct benefits to participants, apart from the opportunity to contribute to the design of a personalized messaging tool for patients with type 2 diabetes. Participation will not pose any associated risks, as it will simply involve expressing their opinions and preferences regarding the proposed intervention.