Study Protocol and Statistical Analysis Plan

Protocol Title

SIMAP: Automatic Association System and Medical Instructions to Pictograms to Facilitate Understanding and Retention.

Sponsor

University of Concepción (Chile)

ClinicalTrials.gov Identifier

NCT05609760

Principal Investigator

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Version Date

05-01-2024

Note

The text below is excerpted from the Institutional Review Board (IRB) protocols established for this study, originally granted approval on November 12, 2019, for implementation in Valparaíso city, and later extended to Hualpen and Talcahuano cities in Chile on December 23, 2019. Unfortunately, the progression of the COVID-19 health crisis led to the suspension of this study. In response to the unprecedented circumstances, the study protocol underwent necessary amendments related to COVID-19 before resuming. The revised protocol with amendments received approval, and it was registered on the ClinicalTrials.gov platform of the National Institutes of Health of the United States under the identifier NCT05609760.

FONDEF ID19I10120

Study Protocol

1. Background and objectives

1.1. Background

The current shift from paternalistic to participatory models of care emphasizes the role of patients and their environment in healthcare decision-making. Effective communication is vital for achieving treatment goals, but various factors can impede patients' comprehension and retention of information, essential for treatment adherence. During clinical-patient communication, especially in post-check-up or discharge instructions, healthcare professionals often convey complex information briefly, overwhelming patients. Studies reveal that 40-80% of information is immediately forgotten, with up to 50% remembered inaccurately. This not only jeopardizes treatment adherence but also exposes patients to risky behaviors. Older adults tend to forget a significant percentage (40-80%) of information provided by healthcare personnel. Addressing communication challenges is crucial to enhancing patient understanding and, consequently, treatment outcomes.

1.2. Objectives

1.2.1. General objective

Develop and evaluate an automatic association system of medical instructions to pictograms to positively impact the understanding, retention, and adherence to treatment for patients diagnosed with bronchial asthma receiving care at primary health centers.

1.2.2. Specific Objectives

- Develop the SIMAP system to automatically complement medical instructions with pictograms in the context of managing and treating bronchial asthma, ensuring interoperability with existing EHRs
- Validate the impact of SIMAP on understanding, retention, and therapeutic adherence among patients consulting at an Asthma respiratory Units (ARU) through a randomized clinical trial.

2. Research Methodology for Clinical Validation

2.1 Clinical Trial Description

In order to determine the effects of implementing a pictogram platform to facilitate understanding and therapeutic adherence, a randomized parallel-group, triple-masked clinical trial will be conducted with patients recently diagnosed with asthma (<=15 days) who enter the Asthma respiratory Units (ARU), hereinafter referred to as ARU, at the Family Health Centers (CESFAM) belonging to the Municipal Health Corporations of the cities of Valparaíso, San Antonio, Hualpén, and Talcahuano. This protocol has been drafted in accordance with the 2010 CONSORT statement (CONSORT 2010).

2.2 Participants

2.2.1 Verification of Inclusion and Exclusion Criteria

All participants in this study will be patients who enter the Asthma respiratory Units (ARU) of the CESFAM belonging to the Municipal Corporation of Valparaíso, Municipality of San Antonio, Municipal Corporation of Hualpén, and Health Administration Directorate of the Municipality of Talcahuano. The selection criteria for study participants are:

Inclusion Criteria

- Adult patients aged 18 to 65 years with a recent diagnosis of bronchial asthma (<=15 days) based on the 2018 criteria from the Global Initiative for Asthma (GINA) (Reddel et al., 2015), recommended by the Ministry of Health of Chile.
- Clinically substantiated diagnosis with spirometry results compatible with the guidelines of GINA.
- Patients initiating bronchodilator treatment, including at least one inhaled corticosteroid and a short-acting bronchodilator.

Exclusion Criteria

- Patients with obstructive bronchial pathology other than bronchial asthma (chronic obstructive pulmonary disease, mixed states, etc.),
- Patients who participated in the design phase of the pictograms (Stage 1 of the project),
- Patients with a diagnosis of dementia, harmful alcohol consumption, and other drug-related diagnoses according to the International Classification of Diseases (ICD-10),
- Patients with significant ophthalmological pathology that hinders the use of pictograms,
- Patients who do not wish to participate in the project.

2.3 Clinical Intervention

2.3.1 Recruitment

A healthcare professional designated by the Director of the CESFAM will be responsible for reviewing the selection criteria for patients entering the ARU during the recruitment period. Upon the first visit (patient's entry into the ARU), if the patient meets the selection criteria, the professional designated by the CESFAM director will introduce the project to the patient and inquire if they would like to meet with the researchers for an invitation to participate in the project by signing the informed consent form. If the patient agrees, the healthcare professional designated by the CESFAM director will inform the project director or a team member designated by her.

Following this, the clinical professional (recruiter) hired by the project will formally invite the patient to participate through the reading and signing of the informed consent. After signing the informed consent, the clinical professional employed by the project (recruiter) will proceed to conduct an interview with the participating patient to obtain a bio-sociodemographic profile, including demographic variables such as gender and age, nationality, time with asthma symptoms, educational level (categorized as basic, middle, higher, and postgraduate education), number of drugs in use, morbidity history as established by the Charlson Comorbidity Index,

smoking history with the corresponding pack-years index, and drugs in use. The initial interview will be conducted by a clinical professional employed by the project. Once the profile is completed, the same clinical professional employed by the project will record the level of disease control at the beginning of the study (time of patient participation acceptance - T0), based on the Asthma Control Test (ACT) questionnaire. This questionnaire has been selected based on its diagnostic capabilities, validation in the Spanish language, and widespread use in both traditional clinical practice and asthma research in Chile. It is currently recommended in national clinical guidelines to establish the level of disease control (Schatz et al., 2006; Vega et al., 2007). ACT scores are established based on 5 questions on a 5-point Likert scale, where higher scores indicate better disease control. Patients with scores above 19 points are considered to have well-controlled asthma.

2.3.2 Assignment to intervention group A or control group B

- Patients will be randomized using a permuted block method to receive one of two possible intervention strategies A or B.
- The permuted block technique aims to ensure a periodic balance in the number of subjects assigned to each intervention or control group (Molina et al., 2015).
- The random assignment sequence will be generated by technical staff of the project with the support of a statistician.

Intervention Group A: This intervention involves utilizing a pictogram system named SIMAP (Automatic Association System of Medical Instructions to Pictograms), which was developed during the initial phase of the study. In essence, SIMAP comprises a series of pictograms intended to enhance the understanding of medical instructions provided by the healthcare team regarding asthma management. The pictograms will be designed by a panel of experts, as detailed in the previous sections of the project, and validated among adult patients consulting in the same population where this study will be implemented. The designed pictograms are specifically tailored to certain elements within the management of bronchial asthma.

This intervention entails furnishing the patient with the instruction sheet given by the clinical staff of the CESFAM as part of their care, but supplemented with pictograms (automatically generated by SIMAP). The provided instructions include images supporting guidance for recognizing bronchodilators, indicating their method of use (daily dose, usage schedule, or as needed), specifications of bronchodilator families with their functions (disease-controlling and symptom-relieving drugs), inhalation technique of bronchodilators, and the use of an inhalation chamber in the process.

The pictograms will be administered by the clinical professional of the CESFAM designated by the Director or by the clinical professional hired by the project (recruiter). This depends on the care process of the CESFAM participating in this study and the availability of hours of the clinical professional of the CESFAM designated by the Director to support the project.

Control Group B: This corresponds to those patients selected and who agreed to participate in the study but will not be assigned to receive the SIMAP system (control group) through the randomization method. These patients will receive their medical instructions in the usual manner, as established by the healthcare team of the participating clinics. Additionally, these patients will receive an informative brochure on bronchial asthma, provided as part of the

standard education when explaining the disease. These brochures will be crafted using everyday language in Spanish, without incorporating pictograms into their content.

The research team will not intervene in any way in the selection of bronchodilators by the healthcare team or in any other decision-making regarding the management of bronchial asthma among participating patients.

2.3.3 Training for those providing interventions A and B

The clinical and technical team of the SIMAP project will train the clinicians working in the participating ARUs of the project in the clinical trial and use of SIMAP. Two training sessions of 30 minutes each, delivered in groups, are planned. In the first of these sessions, an explanation will be provided about the intervention, as well as essential principles regarding how pictograms would facilitate users' understanding of the instructions. The second session will involve the direct application of these pictograms to simulated patients under the guidance of the SIMAP design team.

2.3.4 Follow-up (procedure developed in the same way for both Group A and B)

The follow-up will be conducted according to what is shown in Table I.

Table I: Follow up procedure beginning (t0), 7 days (t1), 30 days (t2) and 60 days (t3)

					Study Period			
		CESFAM Professional	Clinical professional hired by the project (recruiter)	Clinical professional hired by the project (follow-up)	t0	t1	t2	t3
Recruitment	Application of Eligibility Criteria	X			X			
	Informed Consent Signature		X		X			
	Bio-sociodemographic Profile		X		X			
	Charlson Index		X		X			
	ACT test		X		X			
Intervention A	Delivery of instructions with Pictograms	X	X		X			
Intervention B	Delivery of informative brochure		X		X			
Follow-up	ACT test			X		X	X	X
	Inhalation			X		X	X	X

	Technique Adherence Guideline							

3. Data & Statistical Analysis Plan

3.1. Outcomes

The primary outcome of the study consists of the difference in disease control level 60 days after the start of the study, as assessed by the ACT questionnaire. As co-primary outcomes, the same score difference observed at 7 and 30 days after the intervention has been established, as well as adherence to the recommendations provided by the healthcare team regarding the correct inhalation technique for bronchodilators and the use of inhalation chambers within the same time frames. Secondary outcomes of the study include the recognition of the function of bronchodilators. To check adherence to the correct application of the inhalation technique, the project clinician will conduct an assessment of the correct use of the prescribed inhalation therapy according to a checklist developed 10 months after the start of the project. The checklist was developed following the recommendations of national clinical guidelines, the Spanish Association of Pediatrics in Primary Care, and a study conducted by Santo Tomás University on inhalation techniques in asthmatic patients (Manríquez et al., 2015).ris

Additionally, secondary outcomes will include the occurrence of urgent care visits, hospitalizations related to the disease, and the need to escalate bronchodilator therapy as per GINA guidelines at 60 days. Information regarding these secondary outcomes will be extracted from the individual medical records of each patient, as well as during the final follow-up interview when the ACT questionnaire is administered.

3.2. Sample Size

In this stage, we will be working with new patients entering the ARU. Based on the actual population size of adult patients with bronchial asthma recorded from 2019 to 2021 in the participating centers of the project, we have considered a minimum sample size of 48 patients, with a 10% margin of error and a 95% confidence level. We anticipate recruiting this sample within a period of no more than 6 months from the entry of the first patient. The sample calculation takes into account the years during which the COVID-19 social and health crisis occurred. Additionally, due to the lack of previous literature on the evaluation of pictograms for asthma control, it is not feasible to calculate a sample size based on the effect size to be achieved. Ideally, we aim for a homogeneous sample according to the a priori population of entries for each participating center. However, in case of recruitment difficulties at any health center, the sample will be obtained based on the center with the highest availability of patient entries that meet the selection criteria. Considering the measurement of the primary and co-primary outcomes, we plan to randomize a minimum of 48 patients for Stage 2 of the clinical validation of SIMAP.

3.3. Masking

The clinical professionals hired by the project who assess patients during follow-up, statisticians, and study sponsors will be kept unaware of the treatment assignments. Masking of participating patients will be carried out by providing an informative brochure on bronchial

asthma, given as part of the standard education when explaining the disease. These informative brochures will be crafted using everyday language in Spanish, without incorporating pictograms into their content.

3.4. Analysis Strategy

The statistician hired by the project will conduct the data analysis for Stage 2 of the study. Descriptive analysis will initially involve means, standard deviation, absolute and relative frequencies. For inferential analysis, either Student's t-tests or Mann-Whitney tests will be employed to compare means based on the distribution and variances of the obtained data. The Fisher's Exact Test will be used for evaluating qualitative variables.

The primary outcome will be assessed concerning the difference in mean scores observed in bronchial asthma control questionnaires (ACT) between groups at each time point through a profile analysis. The secondary outcome will be evaluated based on the proportion of patients adhering to recommendations regarding the correct use of bronchodilators between both groups. Any intra-group comparisons of qualitative data will be conducted using the ANCOVA or Kruskal-Wallis statistic, depending on the distribution of quantitative data.

All analyses will be carried out by a statistician unaware of the treatment assignment of the participants. Outcomes will be analyzed on an intention-to-treat basis (intervention or control group). In the event of an imbalance in the characteristics of the groups established by the randomization process, potential adjustments to the models will be made. Any model generated will consider the presence of potential interactions between independent variables during its design. Maximum likelihood principles will be ensured based on residual analysis.

To preserve the intention-to-treat principles, missing data will be handled using multiple imputation techniques. All analyses will be performed by a masked statistician using R Project software.

3.5. Data management

and sensitive data of the patients. To achieve this, the collected information will be managed on paper and stored in cabinets kept in the office of the director or alternate director, both of whom will have keys. The Director and Alternate Director are considered the custodians of the data for the Biobío and Valparaíso regions, respectively.

The information collected by the developed system will be encrypted during transfer and storage, ensuring the protection of data privacy. Despite lacking patient identification and being only a set of instructions filtered by diagnosis, the data obtained from the EHR will also be stored on secure servers under a firewall. Project team members with access to this data will sign a confidentiality and proper data handling agreement.

Both the Director and Alternate Director of the project may authorize other team members to access the data for the purposes of necessary analyses to fulfill the objectives of this study. Team members granted access to the generated data will sign a confidentiality and proper data handling agreement.

4. Other Information

Clinical Trial Registration: Once approved by an Ethical-Scientific Committee, the research team of the project will register the study on the ClinicalTrials.gov platform of the National Institutes of Health in the United States.

Funding: This project, which includes the clinical validation of pictograms through a randomized clinical trial, is funded by the National Commission for Scientific and Technological Research through its FONDEF competition, with approval code ID19I10120.

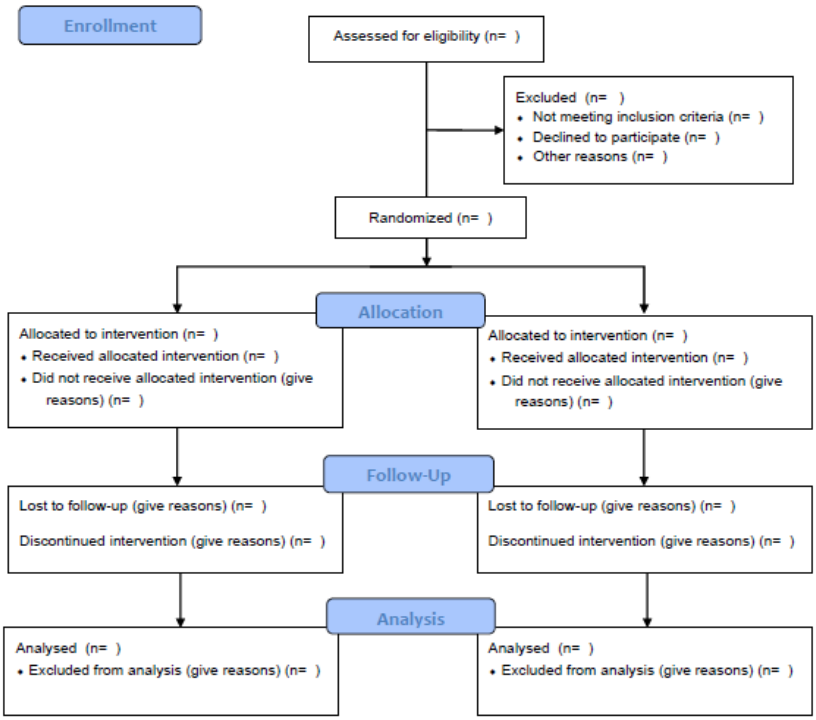

Figure 1: CONSORT diagram. A blank CONSORT diagram to record the number of participants enrolled, number allocated to the treatment arm, number lost to follow-up, and number analyzed

References

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