

# STUDY PROTOCOL

Project to enhance Dermatology E-Consultations in Primary Care Centres using Artificial Intelligence Tools.

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## 1. Abstract

<b>Sponsor Identification</b>	Instituto de Investigación Sanitaria Puerta de Hierro Calle Manuel de Falla 1, 28222, Majadahonda
<b>Study Title</b>	Project to enhance Dermatology E-Consultations in Primary Care Centres using Artificial Intelligence Tools.
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	Puerta de Hierro Majadahonda University Hospital
<b>Investigational centers</b>	Puerta de Hierro Majadahonda University Hospital Majadahonda Health Center Pozuelo Health Center
<b>Ethics Committee</b>	Research Ethics Committee of the Puerta de Hierro Majadahonda University Hospital
<b>Primary Objective</b>	The main objective of this study is to validate the clinical utility of the Legit.Health platform developed by AI LABS GROUP SL in the management of patients with skin pathology by primary care physicians and dermatologists of the Puerta de Hierro Majadahonda University Hospital involved in the project.
<b>Design</b>	Prospective observational analytical study of a series of clinical cases with a longitudinal character.
<b>Disease under study</b>	Patients suspected of having the following pathologies in Primary Care: tumor pathology, inflammatory pathology, and infectious pathology
<b>Study Population and Total Number of Subjects</b>	100 adult patients attending their primary care center with tumor pathology, inflammatory pathology, or infectious pathology.
<b>Calendar. Planned Duration of the Study</b>	The study will last 5 months, with 4 months of recruitment time and 1 month for data analysis.
<b>Ethical Considerations</b>	The development of the study will comply with international Good Clinical Practice (GCP) guidelines, the Declaration of Helsinki in its latest active amendment, and applicable international

	and national rules and regulations. The study will not begin until approval has been obtained from the Ethics Research Committee of the Hospital Universitario Puerta de Hierro Majadahonda.
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## 2. Theoretical framework. Problem statement.

### Background and rationale

Skin-related diseases are a frequent reason for consultation in primary care (PC)<sup>1</sup>; some studies estimate this at approximately 5% of all consultations, mainly among the working population.

This represents a considerable consumption of resources and makes an efficient approach to these conditions a key step in optimizing the functioning of primary care.

Numerous studies show discrepancies in opinion between primary care physicians and dermatologists<sup>2</sup>, with agreement rates in their diagnoses ranging from 57% to 65.52% depending on the study. In general, primary care physicians do not demonstrate adequate knowledge about skin diseases, their diagnosis, and their treatments.

This human limitation when evaluating skin diseases is also reflected in the effort and time required to estimate the degree of involvement in a patient or the stage of the pathology. So much so, that it ends up being a very unrewarding task and can lead to poor adherence to the protocol and inappropriate referrals. Time consumption is especially concerning given that the number of medical professionals, particularly in dermatology, is insufficient to meet the existing demand. Access to a dermatology specialist for the general population is complicated due to the low number (3 dermatologists per 100,000 inhabitants)<sup>3</sup>, a situation that is even more difficult in small population centers. Because of this, screening for dermatological lesions must be carried out by primary care physicians, whose diagnostic capacity is even lower and which may increase the risk of misdiagnosis.

In this regard, the literature shows a discrepancy of between 55% and 65% between primary care physicians and specialists, and studies confirm several expected characteristics: common dermatological diseases are often not recognized or are misdiagnosed by non-dermatologists due to the particular profiles of common diagnoses in this field (drug-induced rashes, fungal infections).

In addition to these inherent limitations, when the preliminary examination is performed by the patient, the possibility of bias arises. This is especially true

when the patient knows that the treatment they receive will be determined by the information they provide. Furthermore, the medical team lacks the means to verify the accuracy of the values reported by the patient, preventing external verification.

For several years, and as part of the objectives of utilizing new information and communication technologies (ICTs), healthcare information systems have been adapted to record certain Primary Care (PC) activities. Since June 2020, an asynchronous e-consultation for Dermatology has been available, allowing the transmission of clinical information and images generated in Health Centers to the Dermatology Department of Puerta de Hierro Majadahonda Hospital, integrated within the hospital's own information system (Selene).

The gradual implementation of teledermatology within the strategic plan of the Community of Madrid has culminated in the development of the teleDERMADRID project. Led by Pilar Sánchez Pobre Bejarano and Manuel Grandal Martín (GAOAIO), in coordination with DGASA, this project enables a new, non-face-to-face consultation modality adapted to the current social and technological reality. This new modality includes an image acquisition management (IAM) tool, accessible via a QR code on the mobile device, which improves and streamlines the e-consultation. This tool is directly linked to the integrated request system (SIPE), ensuring rapid and generally satisfactory access to and response to the health problems of the target population, thus avoiding diagnostic delays, unnecessary travel, and expediting the therapeutic requirements available in our service portfolio.

The reduction of pressure on in-person hospital consultations directly contributes to lower costs for conventional care. All of this is achieved without compromising the humanization of patient care, another key objective for improving health-related quality of life. In addition to the image management tool, a clinical form is associated with the necessary items to complement the image.

Advancing the development of ICTs, the emergence of Artificial Intelligence in medicine has enabled the automation of a wide variety of processes, such as patient triage, allowing for faster care for those suffering from more serious conditions. The use of these types of systems by primary care physicians can increase their diagnostic capacity by up to 12%, proving highly useful in appropriate referrals for patients with skin conditions.

Therefore, this study aims to clinically validate a novel artificial intelligence tool to increase the appropriateness of referrals from primary care to dermatology.

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## Research Questions

The questions this study seeks to answer are the following:

- Does dermatological artificial intelligence help primary care physicians treat patients with skin problems?
- Does Legit.Health's cutaneous artificial intelligence contribute to appropriate referrals?
- Do primary care physicians value the incorporation of dermatological artificial intelligence into their routine clinical practice?

## Hypothesis

The hypothesis guiding this study is that the Legit.Health platform, developed by AI LABS GROUP SL, significantly increases the appropriateness of referrals to dermatology.

This hypothesis is based on the notion that artificial intelligence introduces several significant changes to the diagnostic process:

- Greater sensitivity and specificity than a primary care physician in diagnosing skin conditions, especially in differentiating between malignant and benign lesions.
- It provides the security of a clinically validated second medical opinion.

## 3. Primary and secondary objectives

The main objective of this study is to validate the clinical utility of the Legit.Health platform, developed by AI LABS GROUP SL, in the management of patients with skin conditions by primary care physicians and dermatologists at the Puerta de Hierro Majadahonda University Hospital involved in the project.

Secondary objectives include:

- Reduce and correct the referral of patients with skin conditions from primary care to dermatology.
- Personalize and improve continuing education for primary care physicians in the field of dermatology.
- Offer healthcare adapted to technological innovations.
- Measure the satisfaction of primary care physicians with the Legit.Health platform.
- Measure the satisfaction of dermatologists with the Legit.Health platform.

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## 4. Methods

### Study design

This is a prospective, observational, analytical study of a series of clinical cases.

It is a longitudinal study.

### Study population. Inclusion & exclusion criteria

Adult patients ( $\geq 18$  years) with skin pathologies.

#### Inclusion criteria:

- Patients with suspected of having the following pathologies in Primary Care:
  - Tumor pathology
    - Benign
      - Histiocytoma
      - Seborrheic keratosis
      - Angiomas
    - Precancerous
      - Actinic Keratosis
    - Suspected malignancy:
      - Basal cell carcinoma
      - Squamous cell carcinoma
    - Pigmented lesions
      - Melanocytic nevus
      - Malignant melanoma
  - Inflammatory pathology
    - Psoriasis
    - Atopic dermatitis
    - Urticaria

- Hidradenitis suppurativa
- Lichen planus
- Infectious pathology
  - Viral warts
  - Molluscs
  - Herpes simplex
- Patients aged 18 years or older.
- Patients who have signed the informed consent for the study.

**Exclusion criteria:**

- Patients under 18 years of age.
- Pregnant patients.
- Patients who, in the researcher's opinion, will not comply with the study procedures.

**Variables**

The main variable aims to determine the clinical utility of the platform developed by AI LABS GROUP SL in the management of patients with skin pathology by primary care physicians and dermatologists of the Puerta de Hierro Majadahonda University Hospital involved in the project.

For this purpose, clinicians will complete the **Clinical Utility and Satisfaction Questionnaire (Annex I)**.

In addition, the following secondary variables will be collected::

- Patient demographics:
  - Sex
  - Age
- Teleconsultation data:
  - Response time
  - Response label (follow-up in primary care, shared follow-up, dermatology follow-up, insufficient or inadequate information)
- Data from the in-person consultation:

- Duration of an in-person dermatology appointment to respond to an online primary care consultation.
- Waiting time until being seen in a specialized dermatology clinic.
- Diagnosis
  - Diagnostic correlation between primary care and dermatology.
  - Number of patients referred by pathology.
  - Diagnostic correlation between primary care, dermatology, and dermatopathology (if applicable).
  - Time elapsed between the day of the primary care visit and the day of the histopathological diagnosis (if applicable).
- Primary care physician satisfaction using the Clinical Utility and Satisfaction Questionnaire (Appendix I).
- Dermatologists satisfaction using the Clinical Utility and Satisfaction Questionnaire (Appendix I).

### **Expected sample size**

This study will recruit 100 patients. This study is designed as a proof-of-concept pilot study in which the sample size has been estimated based on the number of primary care physicians who treat patients diagnosed with skin diseases who can be seen in the primary care services of the following centers:

1. Majadahonda Health Center
2. Pozuelo Health Center

During the study recruitment period, all patients diagnosed with skin diseases who meet the selection criteria will be included.

To ensure that all primary care physicians participating in the study have sufficiently interacted with the tool, a minimum of 50 patients per primary care center is required.

The data collected from these patients during the study period will be analyzed, and based on the results, an assessment will be made as to whether it is necessary to expand the sample size to include more patients.

### **Quality control**

The researcher will guarantee the accuracy and integrity of the data, as well as all required reports. Data included in the Data Collection Booklet (DCB) that are derived from source documents will be consistent with those documents; otherwise, any discrepancies will be justified.

The investigator will retain the study documents for at least five years after the study's completion.

Upon request from the monitor, auditor, Ethics Committee, or health authority, the investigator will make all study-related files available, allowing direct access to the source data or documents for monitoring, auditing, Ethics Committee review, and trial inspection by the competent authorities.

### **Limitations of the design, the information source, and the analysis methods**

The main limitation of machine learning lies in the quantity and quality of the images collected. Variability in lighting, color, shape, size, and focus are crucial, as is the number of images per patient. This means that high variability within the same patient and an insufficient number of images to reflect that variability can result in lower-than-expected accuracy.

## **5. Work plan (tasks, milestones and study timeline)**

### **Recruitment of practitioners**

The Principal Investigator and/or the collaborating researchers assigned to this task will explain to the primary care physicians what their participation in the study will entail. The physicians will then be able to ask any questions they deem necessary to clarify any doubts they may have regarding the study. Likewise, all physicians participating in the study will receive specific information on the use of the artificial intelligence tool, provided by an expert in the field.

If the physician wishes to participate in the study, they will sign the Informed Consent form and will be assigned a study code. After signing the informed consent form, the data collection process begins.

The Principal Investigator and/or the collaborating researchers assigned to this task will collect demographic data (age, center, years in practice) and explain to the physician the steps they must follow as part of the study.

### **Patient identification.**

The primary objective of this study is to evaluate the clinical utility perceived by physicians; therefore, patients' clinical variables are not the focus of the study. Patients will be identified in the tool solely for the purpose of enabling its use, and their data will not be analyzed or processed in any way.

The primary care physician will explain the study to the patient using the Patient Information Sheet. The patient will then be able to ask any questions they may have to clarify any doubts regarding the study.

If the patient wishes to participate, they will sign the Informed Consent form and will be assigned a study code. Data collection begins after the informed consent form is signed.

The Principal Investigator and/or the collaborating researchers assigned to this task will enter demographic data (age, sex) and data related to the diagnosis, characteristics, and treatment of the pathology into Legit.Health platform.

## **Procedures to be performed by the primary care physician**

### **1. Consultation**

Primary care physicians will need to take photographs showing the areas affected by the condition. These photographs will be taken with their own smartphone or using a mobile dermatoscope if its use is clinically relevant. Primary care physicians will upload the photographs to the Legit.Health platform.

Primary care physicians will assess the patient's condition through direct observation and guided by the results from the platform. They will enter the diagnosis into the Legit.Health platform by selecting the condition if it is among the first 5 or by using a drop-down menu that displays a wide range of conditions.

In addition to the most likely diagnoses, physicians will have access to referral criteria, the clinical referral questionnaire, and basic treatment advice. When they deem it necessary, they will refer the patient in their Selene system, as they normally would; not through Legit.Health.

### **2. Completion of the questionnaires**

Primary care physicians will complete the Clinical Utility and Satisfaction Questionnaire (Annex I) twice during the study, the first time at 2 months and the second time at 4 months from the start of the study.

## **Procedures to be performed by the specialist physician**

### **1. Consultation**

The Principal Investigator will see patients while maintaining their standard clinical routine. In the Data Collection Document (DCD), they will note the appropriateness of the patient referral. If they deem the referral to dermatology inappropriate, this will also be recorded. The initial diagnosis provided by the primary care physician, as well as their own diagnosis, will be documented. If relevant, the pathology diagnosis will also be included.

### **2. Completion of questionnaires**

Dermatologists will complete the Clinical Utility and Satisfaction Questionnaire (Annex I) twice during the study, the first time at 2 months and the second time at 4 months from the start of the study.

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## 6. Ethical considerations

### **Ethical considerations, regarding information to subjects and informed consent**

The study will be conducted in accordance with international Good Clinical Practice guidelines, the Declaration of Helsinki in its latest amendment, and applicable international and national rules and regulations. It will not commence until it has received approval from the Research Ethics Committee of the Puerta de Hierro Majadahonda University Hospital. Any modification to this protocol will be reviewed and approved by the Principal Investigator and must be evaluated by the Ethics Committee for its approval before enrolling subjects in a modified protocol.

The study will be conducted in accordance with European Regulation 2016/679 of 27 April, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data, and Organic Law 3/2018 of 5 December, on the Protection of Personal Data and Guarantee of Digital Rights, with regard to data processing. No data that allows for the personal identification of subjects will be included, and all information will be managed in a coded manner.

Patients will be informed orally and in writing about all aspects of the study, adapted to their level of understanding. Patients will be given a copy of the informed consent form and information sheet. The investigator must allow patients sufficient time to ask questions about the details of the study.

The preparation of the informed consent form is the responsibility of the Principal Investigator. This form must include all elements required by the International Conference on Harmonisation (ICH), current regulatory guidelines, and comply with Good Clinical Practice (GCP) guidelines and the ethical principles derived from the Declaration of Helsinki.

The investigator, or a person designated by the Principal Investigator, will keep the original signed informed consent form in a secure, restricted-access area, under the custody of the Principal Investigator. This form will never leave the facility, and a copy of the original signed form will be given to the patient.

### **Considerations on the treatment of biological samples**

Biological samples will not be collected in this study.

### **Data confidentiality**

Regarding the confidentiality of the study data, the provisions of Organic Law 3/2018, of December 5, on the Protection of Personal Data and Guarantee of Digital Rights and Regulation (EU) General Data Protection Regulation 2016/679 will be followed.

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## **Interference with the practitioner's prescribing habits**

The clinical management of patients will be adapted to the treatment standards of the Dermatology Service of the Puerta de Hierro Majadahonda University Hospital, without the performance of this study influencing such process.

## **7. Plan for disseminating the results**

Following the completion of the study, the results of the clinical utility and satisfaction surveys, conducted according to the model in Annex I, may be presented at conferences and scientific meetings with prior authorization from both parties. Press releases and communications may also be issued to communicate the study results. All publications and communications must be accepted and approved by Novartis and the Puerta de Hierro Majadahonda University Hospital.

## **8. Protocol modifications**

Any modification to the study protocol will always take the form of a written amendment or addendum. Formalization will require the approval of all individuals responsible for the study. In the case of significant modifications, express approval from the Clinical Research Ethics Committee will be requested.

## **9. Practical considerations**

### **Start, progress and end reports**

The ethics committee will be notified of the start of the study. Annual progress reports will be submitted subsequently.

After the study's conclusions are reached, a final report will be prepared and submitted to the ethics committee.

## **10. Bibliography**

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## 11. Annexes

### Annex I - Clinical Utility and Satisfaction Questionnaire

Based on their experience, without needing to consult the Medical History:

1. Average weekly number of patients with skin conditions you have seen in your practice during the last two months (approximate).
2. Name the conditions for which Legit.Health has been most useful in your daily clinical practice.
3. In your opinion, indicate the impact of Legit.Health from 0 to 10 (where 0 is “no impact” and 10 is “great impact”) on the accuracy of your diagnostic decisions for each of the following diseases:
  - a. Urticaria
  - b. Psoriasis
  - c. Hidradenitis Suppurativa
  - d. Melanoma
  - e. Atopic Dermatitis
  - f. Other (add any other diseases where the tool has had an impact at this point and rate the impact from 0 to 10)
4. In your opinion, please indicate the impact of Legit.Health from 0 to 10 (where 0 is “no impact” and 10 is “great impact”) in relation to reducing the time to issue your diagnostic decision for each of the following diseases:
  - a. Urticaria
  - b. Psoriasis
  - c. Hidradenitis Suppurativa
  - d. Melanoma
  - e. Atopic Dermatitis
  - f. Other (add any other conditions where the tool has had an impact at this point)
5. In your opinion, please indicate the impact of Legit.Health from 0 to 10 (where 0 is “no impact” and 10 is “great impact”) on your therapeutic decision-making, thanks to the included management recommendations, for each of the following diseases:
  - a. Urticaria
  - b. Psoriasis
  - c. Hidradenitis Suppurativa

- 
- d. Melanoma
  - e. Atopic Dermatitis
  - f. Other (add any other conditions where the tool has had an impact at this point)
6. In your opinion, please indicate the impact of Legit.Health from 0 to 10 (where 0 is “no impact” and 10 is “great impact”) on monitoring the evolution of skin lesions for each of the following diseases:
- a. Urticaria
  - b. Psoriasis
  - c. Hidradenitis Suppurativa
  - d. Melanoma
  - e. Atopic Dermatitis
  - f. Other (add any other conditions where the tool has had an impact at this point)
7. In your opinion, please indicate the impact of Legit.Health from 0 to 10 (where 0 is “no impact” and 10 is “high impact”) on the efficiency of interconsultations/referrals to the dermatology service (in cases where referral applies) for each of the following diseases:
- a. Urticaria
  - b. Psoriasis
  - c. Hidradenitis Suppurativa
  - d. Melanoma
  - e. Atopic Dermatitis
  - f. Other (add any other conditions where the tool has had an impact at this point)
8. Please indicate your overall level of satisfaction with the use of Legit.Health from 0 to 10 (where 0 is “not at all satisfied” and 10 is “very satisfied”).

Would you recommend Legit.Health to other primary care colleagues?

In your opinion, please indicate your patients' level of satisfaction with using Legit.Health from 0 to 10 (where 0 is "not at all satisfied" and 10 is "very satisfied").

Would you recommend using Legit.Health to your patients?

Are there any additional features you would consider relevant to include in this tool? Open field

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Are there any features already included in the tool that you consider irrelevant or that do not add value to your clinical practice? Open field