Study title

Estudio piloto para la validación clínica de un sistema DAO (Diagnóstico Asistido por Ordenador) con algoritmos de inteligencia artificial para un seguimiento continuado y remoto de la gravedad de la afectación del paciente de forma objetiva y estable.

Pilot study for the clinical validation of a Computer Aided Diagnosis (CAD) system with artificial intelligence algorithms for a continuous and remote monitoring of the severity of the patient's condition in an objective and stable way.

Protocol code: LEGIT_COVIDX_EVCDAO_2022

Protocol version: Version 2.0, date March 03rd, 2022

PROTOCOL SIGNATURE PAGE

Protocol code: LEGIT_COVIDX_EVCDAO_2022

Product under investigation: Legit.Health Plus

I have read this protocol and agree that it contains all the details necessary for the conduct of the study as described herein. I will conduct this protocol in the manner provided herein, and will make every reasonable effort to complete the study within the time frame designated for it.

I will provide copies of the protocol and all necessary information to personnel participating in the study who will be under my supervision. I will discuss and clarify, to the extent possible, this material with them to ensure that they have complete information about the conduct of the study.

I will provide information about the protocol to the Clinical Research Ethics Committee (IRB) subject to the following conditions: the contents of this protocol may not be used in any other study and may not be disclosed to any other person or entity without the prior written consent of the Principal Investigator. The above shall not apply to disclosure required by government regulations or laws; however, the study coordinator must be notified of such disclosure immediately.

I understand that I may terminate the study or suspend recruitment at any time if necessary to protect the interests of the study subjects. The investigator also has the right to terminate the study with or without cause at any time.

I hereby agree to conduct this study in accordance with all stipulations of the protocol and the Declaration of Helsinki.

Personnel Signature: Principal Investigator

Date	Signature

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1. INFORMACIÓN GENERAL

1.1 Identificación del estudio

Title: Pilot study for the clinical validation of a Computer Aided Diagnosis (CAD) system with artificial intelligence algorithms for a continuous and remote monitoring of the severity of the patient's condition in an objective and stable way.

Protocol code: LEGIT_COVIDX_EVCDAO_2022.

Study design: Prospective observational analytical study of a longitudinal clinical case series.

Product under investigation: Legit.Health Plus

Version and date: Version 2.0, date March 03rd, 2022

1.2 Sponsor

Hospital Universitario de Torrejón, AI LABS GROUP, S.L. y Ribera Salud S.A.

1.3 Principal investigator/Colaborators and center involved

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2. INTRODUCTION AND JUSTIFICATION

The pandemic caused by the new SARS-CoV-2 virus is challenging healthcare systems around the world in different ways. The main focus is on the care of people suffering from COVID-19. In particular, the care of critically ill patients in hospitals and intensive care units has led to bottlenecks in intensive care capacities in some countries.[1]

With the isolation measures in mid-March 2020, health authorities ordered hospitals to postpone all admissions, surgical procedures and planned interventions until further notice, to the extent medically justifiable, not only to free staff and material resources for the treatment of patients with COVID-19, but also to minimize transmissions of the COVID-19 virus between patients and medical staff. Like all other medical disciplines, this also affected dermatology departments in their inpatient and outpatient services. U.S. dermatologists called dermatology practices "vectors of COVID-19 transmission"[2] and recommended the immediate suspension of all "non-urgent" consultations[1]. This, after almost two years, has still not been able to regain its usual flow due to the multiple variety of virus variants that continue to plague the healthcare situation.

Because of this, it is necessary to implement an alternative system so that dermatological patients can continue to be diagnosed with their respective pathologies even more quickly, comfortably and efficiently, and can also have a remote and continuous follow-up of the disease, since many people who have a skin pathology end up going to the doctor when they need to. This is due to the unbalanced ratio of dermatologists to patients in most European countries, including Spain. This fact not only causes pathologies to go unnoticed, but also has deadly effects on patients with skin cancer, especially melanoma, and causes chronic diseases such as psoriasis, eczema or hidradenitis suppurativa to worsen over time, reducing patients' quality of life and increasing the economic impact on each patient. This has been further exacerbated during the COVID-19 crisis, as patients avoid going to the doctor to reduce exposure to the virus.

Unfortunately, as of today there are no reliable tools for remote pathology diagnosis and activity. Therefore, the activity of the condition can currently only be measured by a **specialist physician in consultation**.

In addition, the method currently used to quantify, stage or measure the involvement of patients in consultation has severe limitations. The most indisputable limitation is the **inherent difficulty of human beings to quantify parameters in an objective, stable and precise manner.** In other words, humans have a limited capacity to count lesions,

[1] Elsner P. (2020). Teledermatology in the times of COVID-19 - a systematic review. Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG, 18(8), 841–845. https://doi.org/10.1111/ddg.14180

[2] Kwatra SG, Sweren RJ, Grossberg AL. Dermatology practices as vectors for COVID-19 transmission: a call for immediate cessation of non-emergent dermatology visits [Internet]. J Am Acad Dermatol 2020; 82(5): e179–e180.

quantify the surface area of a lesion or document the redness of an area, to give a few examples.

This human limitation in the estimation of parameters is also reflected in the **effort and time required** to estimate the degree of involvement of a patient or the stage of the pathology. So much so, that it ends up being a very unrewarding task and can result in low adherence to the protocol or limited use of the tool.

On the other hand, the measurement systems in which the professional visually estimates the impairment try to classify the disease by severity using a reduced number of categories, such as: none, mild, moderate and severe. Because of this, the system has a very high **minimum detectable change,** and a very low **sensitivity to change.**

And in addition to these inherent limitations, in cases where the measurement scales are patient-reported, there is the possibility of bias. This is especially true in cases where the patient knows that the treatment he or she receives will be determined by the information he or she provides. In addition, **the medical team lacks the means to ensure that the values reported by the patient are accurate**, which precludes external verification.

Fortunately, in recent years there has been an increasing demand to develop **Computer Aided Diagnosis (CAD) systems** and other systems that facilitate the detection of different pathologies through **algorithms.** CAD systems are an interdisciplinary technology that combines artificial intelligence and digital image processing. Image processing based on complex pattern recognition systems makes it possible for the physician to interpret the information contained in the medical image with much less difficulty. Advances in image recognition and artificial intelligence have led to innovations in the diagnosis of all types of pathologies. It has been demonstrated that through artificial intelligence (AI) algorithms it is possible to classify photographs of lesions with a level of competence comparable to that of a medical expert[3] [4].

Therefore, the use of artificial vision applications when collecting information about the patient's condition presents a huge advance that not only brings **reliability to the documentation process**, but also allows **greater precision when measuring visual signs and quantifying the severity** of the pathology.

Thanks to the Legit.Health platform, patients can be evaluated from home, thus avoiding the risk of contagion among more patients and healthcare professionals, while at the same time monitoring chronic patients to prevent them from getting worse. Likewise, for example, patients with moles are analyzed to ensure that they are diagnosed as

[3] Esteva A, Kuprel B, Novoa RA, et al. Dermatologist-level classification of skin cancer with deep neural networks, Nature. 2017; 542(7639): 115-118.

[4] Haenssle HA, Fink C, Schneiderbauer R, et al; Reader study level-I and level-II Groups. Man against machine: diagnostic performance of a deep learning convolutional neural network for dermoscopic melanoma recognition in comparison to 58 dermatologists., Ann Oncol. 2018;29(8):1836-1842.

premalignant or malignant and treated in time. A solution that empowers patients with a systematic means to monitor their disease and also empowers medical practice by allowing physicians to better assess patients based on a more holistic view of their conditions.
Accordingly, this study aims to clinically validate a novel artificial intelligence tool for activity grading in affected patients.
This innovation has the potential to facilitate medical practice in the treatment of some chronic dermatological pathology and improve the quality of life of patients affected by this pathology. In addition, this technology provides a new measurement tool that opens the door to a new field of research into the effectiveness of treatments or the analysis of the pathology itself and its subtypes.

3. STUDY TYPE AND DESIGN

This is a prospective observational analytical study of a longitudinal clinical case series.

4. OBJECTIVES

4.1 Hypothesis

The hypothesis guiding this study is that the Legit.Health Plus tool (hereinafter the device) with artificial intelligence developed by AI LABS GROUP SL can perform remote monitoring of pathology severity in a continuous and objective manner.

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

1. Remote monitoring of dermatological pathology severity in a continuous and objective manner.
2. Empowerment of the patient with a systematic tool to monitor their own pathology.

In short, the hypothesis of the study is that Legit.Health Plus is a very useful tool to reduce the need for a patient to visit the doctor so often, since it is possible to monitor the evolution of the pathology remotely, thus increasing their empowerment, with the consequent reduction in the number of face-to-face consultations in hospitals.

4.2 Main objective

The main objective of the present study is to validate that the device, based on artificial intelligence and developed by AI LABS GROUP SL, allows to remotely determine the evolution of chronic dermatological pathologies in an objective and stable way, reaching a score of 8 or higher in the Clinical Utility Questionnaire (CUS).

4.3 Secondary objectives

Secondary objectives include:

- To validate that the device generates reliable pathology tracking. That is, it is a reliable system.
- Validate that the device generates patient satisfaction as it can be used remotely.
- Validate that the device contributes to reducing face-to-face consultations.

5. MATERIAL AND METHOD

5.1 Study period

This study estimates a recruitment period of 6 months.

The total duration of the study is estimated at 12 months, including the time required after recruitment of the last subject for closing and editing the database, data analysis, and preparation of the final study report.

The total duration of the study for each participant will be 6 months from the date of inclusion.

5.2 Study design and development

Patients who meet the selection criteria will be offered to participate in the study (see section "Participants").

Patients will be recruited at the Dermatology Department of the Hospital Universitario de Torrejón. Recruitment will be carried out by the Principal Investigator or those collaborating investigators to whom he/she delegates this task.

5.2.1 Patient selection and recruitment visit

The recruitment period will last six (6) months, during which the investigators will enroll patients in the study.

The Principal Investigator and/or the collaborating investigators assigned to this task will explain to the patient what his/her participation in the study will consist of by means of the Patient Information Sheet. The patient in turn will be able to ask all the questions he/she considers appropriate in order to clarify all his/her doubts concerning the study.

If the patient wishes to participate in the study, he/she will sign the Informed Consent Form and will be assigned a study code. After signing the informed consent, the data collection process begins.

The Principal Investigator and/or collaborating investigators assigned to this task will collect demographic data (age, sex, ...) and data related to the diagnosis, characteristics

and treatment of the pathology. Once the information has been completed, he/she will proceed to explain to the patient the instructions for completing the questionnaire and taking photographs in the device, according to the instructions detailed in the "Patient Information Guide" (Annex IV), a copy of which will be given to the patient.

During this first visit, the patient will take the photograph and complete the questionnaire associated with the pathology, if any, in the device under the supervision of the research team, who will ensure that the patient understands the instructions correctly.

After this visit, the patient will take the photographs and complete the questionnaires at home autonomously and telematically, as described in the following section.

The device will be provided free of charge to patients and the research team for the duration of the study and the patient's participation in the study.

5.2.2 Procedures to be performed by the patient at home

5.2.2.1 Completion of questionnaires

Patients will report their pathology autonomously, at home, by completing the questionnaires and following the indications of the research team and the "Patient Information Guide" (Appendix IV) provided during the screening visit.

Periodically, the patient will document the status of his pathology by means of the questionnaires corresponding to each pathology and the DLQI (Appendix V), which are integrated in the device and are filled in, together with the taking of the photograph.

On a bimonthly basis, the patient will complete the "Patient Satisfaction Questionnaire" (Annex II), which asks about general aspects of the user experience. In addition, he/she will complete the System Usability Scale (SUS) Questionnaire (Annex III) at the same frequency.

5.2.2.2 Taking photographs

In the same act, by filling in the questionnaires through the app, the patients will have to take photographs showing the areas affected by the pathology. These photographs will be taken with the patient's smartphone, from their homes and autonomously. These photographs will be filled in with the periodicity established by the specialist doctor in consultation.

No technical camera requirements will be necessary: the photographs will be taken with the camera available on the patient's smartphone.

In this way, patients will send the photographs to the research team telematically through the device, which consists of a web app with the status of a medical device (Annex VII) in which both patients and members of the medical team have access credentials. The Legit.Health team will not have access to the account or patient information.

This transfer of information and the storage of the photographs will be in line with the European Regulation 2016/679 of 27 April on the protection of natural persons with regard to the processing of personal data and the free movement of such data and the Organic Law 3/2018 of 5 December on the Protection of Personal Data and guarantee of digital rights.

5.2.3 Follow-up visits

The follow-up period will last six months. During this period, patients will have at least two follow-up visits, which may be telematic or face-to-face, during the execution of the study.

The Principal Investigator and/or collaborating investigators will also collect the patient satisfaction questionnaire (Annex II) and the System Usability Scale - SUS (Annex III) on a bimonthly basis.

In addition, the Principal Investigator and/or investigators will complete the Clinical Utility Questionnaire (CUS) (Appendix I) and the System Usability Scale (SUS) (Appendix III) on a bimonthly basis.

5.2.4 Advice from the Legit.Health team on the study

The Legit.Health team will assist the research team in the process of taking the photographs and will supervise the labeling of the photographs to ensure that both the photographs and the labeling nomenclature meet the technical criteria necessary for further analysis.

Periodically, the Legit.Health team will meet with the researchers and review the data collected to ensure that the entire collection procedure is carried out correctly.

The periodicity of the reviews follows the following logic:

1. The first review will be performed when samples have been collected from 3 patients.
2. Subsequently, every 5 new patients.

In case the first review requires any correction, a next evaluation of the next 3 patients will be done.

Review meetings will be held according to the availability of the investigator.

6. STUDY VARIABLES

6.1 Main variable

The primary endpoint aims to determine the validity of the DAO system developed by AI LABS GROUP SL to determine that the monitoring of the severity of the pathology is performed in a continuous and objective manner.

For this purpose, clinicians will fill out the Clinical Utility Questionnaire (CUS) (Annex I) provided by Legit.Health.

As explained in the introduction, patient involvement is diagnosed only observationally. For this purpose, when the patient uploads a photo, a new possible diagnosis will be generated that has to be confirmed by the specialist, in case he/she has not yet assigned a pathology. If a pathology has already been assigned, new information on the evolution of the pathology will be generated.

6.2 Secondary variables

- Demographic data: sex, age, zip code.
- Clinical data: diagnosis, date of diagnosis, medication the patient is taking.
- Worsening pathology alerts.
- Quality of life: score of the Dermatology Quality of Life Index or DLQI questionnaire (Annex V).
- Degree of patient satisfaction using the patient satisfaction questionnaire (Annex II).
- Consultation management indicators: number of face-to-face consultations, number of telematic consultations and consultation times.
- Evaluation of the usability of the device by clinicians and patients, using the System Usability Scale (SUS) questionnaire (Annex III).
- Use of the application: logins, photographs sent.

7. PARTICIPANTS

7.1 Study population

Patients with any of the chronic dermatologic pathologies specified in the inclusion criteria and attended at the Dermatology Department of the Hospital Universitario de Torrejón.

7.2 Inclusion Criteria

- Patients with any of the following chronic dermatological pathologies.
    - Psoriasis
    - Urticaria
    - Hidrosadenitis suppurativa
    - Acne

- Atopic dermatitis
- Vitiligo
- Infantile hemangioma
- Nail pathology

- Patients who have signed the informed consent for the study.
- Patients with written and spoken proficiency in Spanish or English.
- Patients with a smartphone, i.e.: a phone with internet access and integrated camera, of any model and technical characteristics.

7.3 Exclusion Criteria

- Patients who, according to the investigator's criteria, will not comply with the study procedures.
- Patients who were already using the tool under study.

8. SAMPLE SIZE

A total of 180 patients will be recruited in this study. This study is planned as a "proof of concept" pilot study in which the sample size has been estimated based on the number of patients diagnosed with any of the pathologies defined in the inclusion criteria. During the recruitment period of the study, all patients with a diagnosis of a chronic dermatologic pathology who meet the selection criteria will be included. The data collected from these patients during the study period will be analyzed, and depending on the results obtained it will be assessed whether it is necessary to increase the sample size to include more patients.

9. RESULTS ANALYSIS

Each variable will be characterized using frequency distributions for qualitative variables and central tendency statistics such as mean and median and variability statistics such as standard deviation (S.D.) or interquartile range for quantitative variables according to their distributional characteristics.

Between-group and within-group comparisons will be made using parametric tests whenever the distributional characteristics of the data allow it. For intergroup comparisons, one- and two-factor Analysis of Variance techniques will be used with post-hoc comparisons if significant overall differences are detected. To assess intra-group changes, Student's t-test for related samples or Analysis of Variance/ANOVA with repeated measures will be used if the theoretical assumptions of the model are supported by the

data. Otherwise, more flexible models (GEE) that allow incorporating different autocorrelation structures of the data will be fitted.

Comparisons between groups with respect to qualitative variables will be carried out by means of contingency tables and Fisher's exact or Chi-square tests. The probability of type I error will not be adjusted for multiple comparisons. The level of statistical significance in the contrasts (alpha) will be 5 percent with bilateral contrasts.

Comparisons between two continuous variables will be made using Pearson's or Spearman's correlation, depending on the distributional characteristics.

Sensitivity, specificity, positive and negative predictive values (PPV and NPV) and likelihood ratios (LR+ and LR-) will be calculated by comparing the results obtained using the Legit.Health tool and the paper questionnaire system used as the gold standard.

Analyses will be performed using appropriate statistical software, SPSS version 23.0 and STATA 13.0. Values of $p<0.05$ will be considered significant.

10. ETHICAL CONSIDERATIONS

The conduct of the study will conform to international Good Clinical Practice standards, to the Declaration of Helsinki in its latest active amendment, and to international and national rules and regulations and will not be initiated until approval has been obtained from the Vinalopó-Torrevieja Ethics Committee. Any modification of this protocol will be reviewed and approved by the Principal Investigator and must be evaluated by the Ethics Committee for approval before including subjects in a modified protocol.

The study will be conducted according to European Regulation 2016/679, of 27 April, on the protection of natural persons with regard to the processing of personal data and 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 in which no data that allows the personal identification of subjects will be included, the information being managed in an encrypted manner.

Patients will be informed orally and in writing about all the information related to the study and adapted to their level of understanding. A copy of the consent form and information sheet should be provided to the patient. The investigator should allow the patient the necessary time to ask questions about the details of the study.

Preparation of the informed consent form is the responsibility of the Principal Investigator. This form should include all the elements required by the International Conference of Harmonization (ICH), current regulatory guidelines, and comply with the Standards of Good Clinical Practice (GCP) and ethical principles that originate from the Declaration of Helsinki.

The investigator or the Principal Investigator's designee will keep the original signed informed consent form in a secure restricted access area under the custody of the

Principal Investigator and will never leave the center and will give a copy of the original signed consent form to the patient.

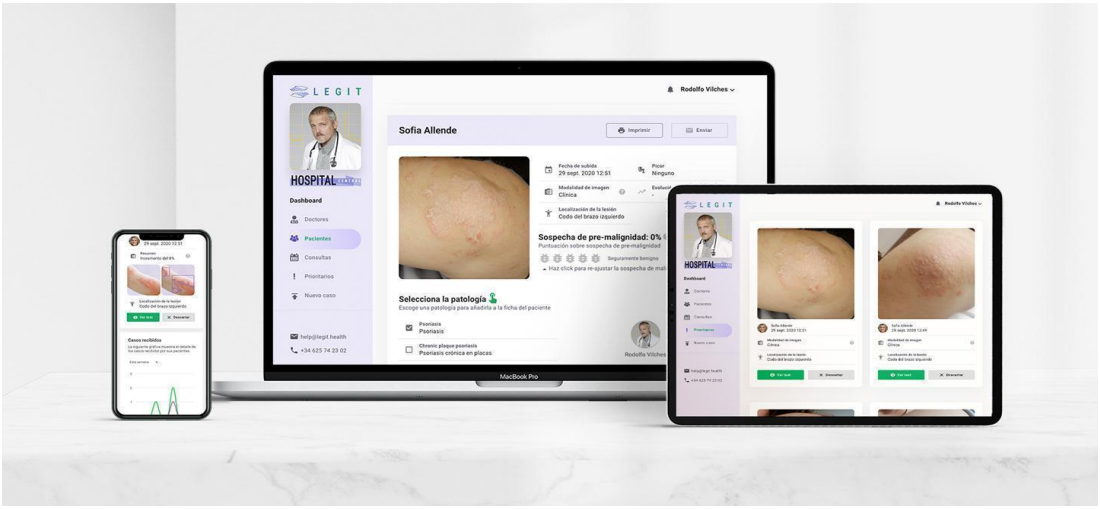
11. PRODUCT DESCRIPTION

Legit.Health Plus is a digital medical device (Annex VII) that helps dermatologists to introduce a detailed and objective follow-up in the skin evaluation process, thanks to the automatic analysis of images and the auto-filling of measurement scales.

Legit.Health is a trademark of the company AI LABS GROUP SL, domiciled in the Basque Country. AI LABS GROUP SL specializes in the use of pioneering machine vision techniques and deep learning algorithms to develop algorithms for classification and severity estimation of visible pathologies, especially in the world of dermatology.

The device performs two types of algorithmic operations, with enormous medical utility. First, the device algorithms are able to diagnose pathologies. Secondly, they are able to track the pathology.

In all cases, the device is a clinical decision support tool, i.e. its purpose is to help doctors in the practice of their profession, reducing their workload and the risk of errors, while patients feel more supported. However, it is not software that a patient can use without medical supervision, but a tool for communication and automation of the relationship between the patient and his doctor.



Software Legit.Health images on different devices.

11.1 Diagnosis

Legit.Health Plus' wide range of diagnostic algorithms allows classification of 232 skin pathologies. Specifically, the device has focused on providing diagnostics for chronic pathologies, because of the burden they place on the healthcare system and the effects on

patients' quality of life, and on malignant and pre-malignant pathologies, because of the danger they pose to the population.

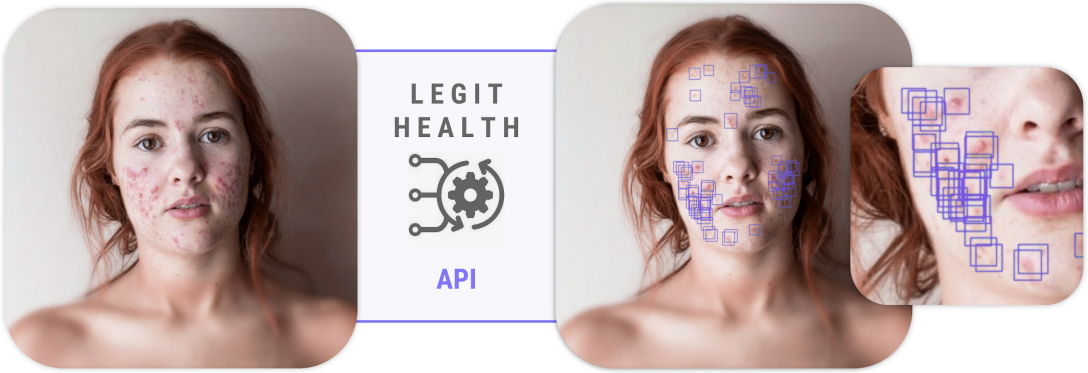
11.2 Follow up

In addition to diagnosis, the device algorithms are able to quantify, through a photograph, visible signs such as erythema or induration of a skin lesion. In addition, Legit.Health has developed algorithms capable of performing wheal and lesion counts. On the other hand, the algorithms make it possible to determine the surface area affected by a particular pathology with high precision.

These algorithms make it possible to track the evolution of a pathology by periodically analyzing the visual information contained in a photograph. This means that patient follow-up is largely automated, resulting in a reduction of the clinical workload.

An example of such tracking algorithms is acne lesion counting. The acne tracking algorithm developed by Legit.Health receives a photograph of the patient and returns numerical values related, on the one hand, to the number of lesions, and on the other hand, to the concentration and density of lesion clusters. This allows an accurate monitoring of the evolution of the pathology, with an extremely high minimum detectable change, far superior to the system currently used in medical practice.

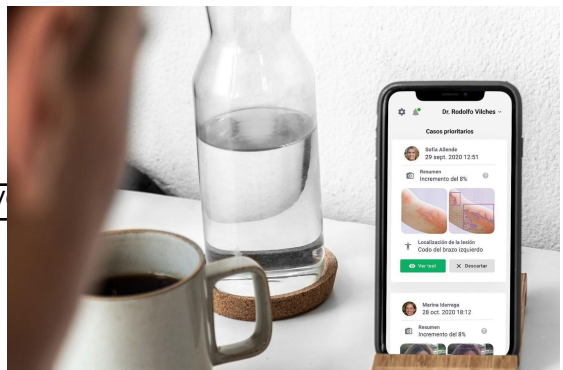
Additionally, the algorithm returns the photograph itself with an explanation of what the algorithm has done, as can be seen below:



This photograph provides great medical value, as it allows the healthcare professional and the patient to understand what the algorithm has done and to quickly detect if the algorithm has made any errors. In other words, it increases the explainability of the algorithm.

In addition, the device collects symptoms that are not visibly noticeable, such as itching, or the different domains of quality of life, through convenient digital questionnaires.

One of the functionalities of the device most valued by physicians is the automatic filling in of scales. In essence: Legit.Health's



algorithms automatically fill in scales by simply looking at images and collecting short questionnaires from patients. In this way, the tool automatically completes most measurement scales, such as UAS7, PASI, SCORAD, BSA, DLQI and many more.

All in all, the device helps physicians optimize the time available within a practice, as doctors can work with the predicted diagnostic data and spend more time ensuring that the patient understands the implications of their disease and the importance of adherence to treatment.

Ultimately, the device gives patients and physicians the ability to track changes in skin lesions that are often gradual and subtle, and to correlate different symptoms to identify triggers or evaluate treatment performance.

In this way, patients gain a more detailed understanding of symptoms, changes, treatment effectiveness and potential triggers.

12. SAFETY

Subjects enrolled in this study will not be exposed to any procedure that could jeopardize their safety.

No adverse reactions related to the investigational product are expected.

13. DATA COLLECTION AND MANAGEMENT

13.1 Source Data Identification

Source documents are understood to be all the observations or notes recorded on the clinical interventions, as well as all the reports and notes necessary for the reconstruction and evaluation of the study's data collection notebook.

Basically, although not exclusively, the source documents are composed of the documents and annotations that form part of the patient's Clinical History and the different surveys to be collected in the center.

Whenever possible, the original document should be kept as the source document; however, it is acceptable to provide a photocopy as long as it is clear, legible and an exact duplicate of the original document.

13.2 Data quality assurance

The Principal Investigator is responsible for reviewing and approving the study protocol and its possible modifications in the future, signing the Principal Investigator's commitment, guaranteeing that the persons involved in the center will respect the

confidentiality of patient information and protect personal data, and reviewing and approving the final study report. All members of the research team will assess the eligibility of the study patients, inform and request written informed consent, collect the source data of the study in the clinical record and transfer them to the Data Collection Forms (CRF) (Annex VI).

13.3 Data management

The management of the collection and processing of the study data will be carried out through the design of a Data Collection Notebook (CRD) (Annex VI), in paper format, in which the investigators assigned to this task will enter the source data of each patient participating in the study.

Current legislation will be complied with in terms of data confidentiality protection (European Regulation 2016/679, of 27 April, on the protection of natural persons with regard to the processing of personal data and the free movement of such data and Organic Law 3/2018, of 5 December, on Personal Data Protection and guarantee of digital rights). For this purpose, each patient will receive an alphanumeric identification code in the study that will not include any data allowing personal identification (coded CRD). The Principal Investigator will have an independent list that will allow the connection of the identification codes of the patients participating in the study with their clinical and personal data. This document will be filed in a secure area with restricted access, under the custody of the Principal Investigator and will never leave the center.

Once the paper CRDs are completed and closed by the Principal Investigator, the data will be transferred to a database.

As in the CRDs, the Database will comply with current legislation in terms of data confidentiality protection (European Regulation 2016/679, of 27 April, on the protection of natural persons with regard to the processing of personal data and 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) in which no data allowing personal identification of patients will be included.

The transfer of data from the paper CRD to the electronic Database will be carried out using the double data entry technique. This will be done by the researchers collaborating in the project.

The data will be managed and tabulated with consistency rules and logical ranges to control inconsistencies during data tabulation. A validation process of the clinical data will be carried out by running computer filters based on validation rules, which will automatically identify missing values or inconsistencies of clinical data according to the protocol. Additionally, manual editing and validation will be performed using descriptive and exploratory statistical techniques to complement the detection of logical errors and inconsistent values.

The Database will be considered closed upon completion of all Data Management processes and satisfactory resolution of discrepancies and errors in the data. Any changes in the databases after its closure can only be made after written agreement between the Principal Investigator and the technical coordinators of the project.

AI LABS GROUP, S.L. (hereinafter Legit.Health) is the owner of the software named "Legit.Health Plus". During the period of validity of this study, Legit.Health will grant a license to use the Legit.Health Plus device to the research team free of charge. The research team will be the administrator of the account created on the Legit.Health platform. Both patients and members of the medical team will have login credentials. The Legit.Health team will not have access to the account or patient information.

The Data Controller is the research team. Legit.Health is the Data Processor and is not responsible for the processing of the data included in the Software or its users.

The storage of data and photographs will be in line with the European Regulation 2016/679 of 27 April on the protection of natural persons with regard to the processing of personal data and the free movement of such data and the Organic Law 3/2018 of 5 December on the Protection of Personal Data and guarantee of digital rights. At the end of the study, all information stored in the device will be totally and permanently deleted.

The Legit.Health platform complies with current legislation on the protection and confidentiality of personal data (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). Appropriate technical and organizational security measures are adopted to ensure the security of personal data and prevent its alteration, loss, unauthorized processing or access, given the state of technology, the nature of the data and the risks to which they are exposed, whether from human action or the natural physical environment.

14. STUDY LIMITATIONS

The main limitation of machine learning lies in the quantity and quality of the images collected. Variability in illumination, color, shape, size and focus are determinants, in addition to the number of images per patient. This means that a large variability within the same patient and an insufficient number of images to reflect that variability may result in a lower accuracy than expected.

On the other hand, it is worth mentioning that the present study excludes from its objectives factors that would play a role in the validation of a new scale for measuring the activity of some chronic dermatological pathology from the device, such as the Minimal Detectable Change or the inclusion of new parameters, such as the exact number of lesions or the diameter of the largest lesion, and focuses on the diagnostic capability of the algorithm and the usability advantages of the tool.

However, it could be expected that a new data collection tool, such as automatic vision algorithms, will open the door to the creation of new measurement scales for some chronic dermatological pathology, whose use was not feasible in the absence of such a tool - either because of the automaticity of data collection, or because of the precision in the calculation of parameters such as the number of lesions, the affected surface or the redness.

15. ANNEXES

ANNEX I. Clinical Utility Questionnaire (CUS)

We want to know your opinion about the usefulness of the Legit.Health application. Please answer the following questions:

1. **Medical Specialty.** Select your specialty.

   Check only one option

☐	Dermatology
☐	Primary health care
☐	Nursery
☐	Auxiliar

2. **Performance.** In your opinion, does the Legit. Health application perform as expected/anticipated for its intended use?

   Check only one option

☐	Yes
☐	No

3. **Ease of use.** In your opinion, please indicate the degree of difficulty in using the Legit.Health application.

   (0 = Very difficult; 10 = Very easy):

Very difficult	0	1	2	3	4	5	6	7	8	9	10	Very easy

4. **Usefulness of the information.** In your opinion, indicate the degree of usefulness of the information provided by Legit.Health for clinical decision making.

   (0 = No useful; 10= Very useful):

No useful	0	1	2	3	4	5	6	7	8	9	10	Very useful

5. **Remote consultations.** In your opinion, and taking into account that when a patient uploads a photo from home and the algorithms process it, it counts as a consultation, how much have you been able to reduce the average consultation time per patient?

   Check only one option

☐	I have not reduced time

- [ ] Between 1 and 4 minutes
- [ ] Between 4 and 8 minutes
- [ ] More than 8 minutes

6. **Resource optimization.** In your opinion, do you think the Legit.Health application has helped you to optimize your time according to the needs of each patient?

- [ ] Yes
- [ ] No

7. **Patient triage.** In your opinion, has the patient prioritization option helped you to better manage patients with higher clinical requirements?

(0 = No help; 10= A lot of help:

No help	0	1	2	3	4	5	6	7	8	9	10	A lot of help

8. **Speed.** In your opinion, how fast do you find the generation of the report with the results of the algorithms?

(0 = Very slow; 10= Very fast):

Very slow	0	1	2	3	4	5	6	7	8	9	10	Very fast

9. **Diagnostic support.** In your opinion, how efficient is the tool in terms of diagnostic support?

(0 = Very inefficient; 10= Very efficient):

Very inefficient	0	1	2	3	4	5	6	7	8	9	10	Very efficient

10. **Constant monitoring.** In your opinion, do you think the Legit.Health application contributes to obtaining more information about the patient's condition?

- [ ] Yes
- [ ] No

11. **Degree of objectivity.** In your opinion, to what degree does the Legit.Health application increase objectivity in patient follow-up?

(0 = A little; 10 = A lot):

A little	0	1	2	3	4	5	6	7	8	9	10	A lot

12. **Overall satisfaction. Indicate the degree of satisfaction with the Legit.Health application for remote monitoring of dermatological diseases.**

(0 = Very unsatisfied; 10= Very satisfied):

Very unsatisfied	0	1	2	3	4	5	6	7	8	9	10	Very satisfied

13. How likely would you be to recommend this service to another professional?

(0 = Surely you would not recommend it; 10= Surely you would recommend it):

Surely you would not recommend it	0	1	2	3	4	5	6	7	8	9	10	Surely you would recommend it

14. Describe in your own words how Legit.Health has helped you manage patients with dermatological diseases.

To calculate the CUS score, the contributions of each item must first be summed. The contribution of each item will be worth between 0 and 10 for all those questions that include a score from 0 to 10. For questions 1, 6 and 10, the contribution will be 0 for no and 10 for yes. For question 5, the option I have not reduced time counts as 0, Between 1 and 4 minutes counts as 4, Between 4 and 8 minutes as 8 and More than 8 minutes as 10. The sum of the results is multiplied by 100 and divided by 120 to obtain the overall SUS value. The result will be between 0 and 100.

ANNEX II. Patient Satisfaction Questionnaire

We would like to know your opinion about the tools used. Please rate from 0 to 10 the following aspects of your experience following the references:

1. **Ease of use:** Do you find the App intuitive and easy to use?

(0 = Very difficult; 10= Very easy):

Very difficult	0	1	2	3	4	5	6	7	8	9	10	Very easy

2. **Usefulness of the App:** Do I find the App a useful tool for tracking your skin disease?

(0 = No useful; 10= Very useful):

No useful	0	1	2	3	4	5	6	7	8	9	10	Very useful

3. **Empowerment: Do you consider that the App has allowed you to have greater autonomy and control in the follow-up of my disease?**

(0 = Strongly disagree; 10= Strongly agree):

Strongly disagree	0	1	2	3	4	5	6	7	8	9	10	Strongly agree

4. **Learning and knowledge:** Do you consider that the tool has provided you with information to learn more about your disease status?

(0 = Strongly disagree; 10= Strongly agree):

Strongly disagree	0	1	2	3	4	5	6	7	8	9	10	Strongly agree

5. **Satisfaction with the care received. How would you rate the treatment received by your doctor through the App?**

(0 = Really bad; 10= Excellent):

Really bad	0	1	2	3	4	5	6	7	8	9	10	Excellent

6. **Support:** Have you felt more supported during the follow-up of your condition thanks to the App?

(0 = I have felt very unaccompanied; 10= I have felt very accompanied:

Very unaccompanied	0	1	2	3	4	5	6	7	8	9	10	Very accompanied

7. **Overall Satisfaction.** Please indicate how satisfied you are with the Legit.Health application for remote monitoring of your condition.

(0 = Very unsatisfied; 10 = Very satisfied):

Very unsatisfied	0	1	2	3	4	5	6	7	8	9	10	Very satisfied

8. **Grade of recommendation:** Would you recommend the use of this app to other patients with a skin pathology like yours?

(0 = I would certainly not recommend it; 10 = I would recommend it):

Not recommend it	0	1	2	3	4	5	6	7	8	9	10	Recommend it

9. Other comments:

Thank you for your colaboration

ANNEX III. System Usability Scale - SUS

Please rate from 0 to 5 the following aspects:

1. I think I **would like** to use this app frequently

Completely disagree <———————————————> Completely agree

0	1	2	3	4	5

2. I found this app **unnecessarily complex**

Completely disagree <———————————————> Completely agree

0	1	2	3	4	5

3. I thought the app was **easy to use**

Completely disagree <———————————————> Completely agree

0	1	2	3	4	5

4. I think I would need help from a **technical expert** to use the app.

Completely disagree <———————————————> Completely agree

0	1	2	3	4	5

5. I found that the **various possibilities** of the APP were quite **well integrated**.

Completely disagree <———————————————> Completely agree

0	1	2	3	4	5

6. I thought there was too much **inconsistency** in the app.

Completely disagree <———————————————> Completely agree

0	1	2	3	4	5

7. I think most people **would learn** to use this app very quickly.

Completely disagree <———————————————> Completely agree

0	1	2	3	4	5

8. I found this app **very difficult to use**.

Completely disagree <———————————————> Completely agree

0	1	2	3	4	5

9. I felt **very confident** using the app.

Completely disagree <———————————————> Completely agree

0	1	2	3	4	5

10. I would need to learn a lot of things **before** using the app properly.

Completely disagree <———————————————> Completely agree

0	1	2	3	4	5

To calculate the SUS score, the contributions of each item must first be summed. The contribution of each point will be worth between 0 and 4. For points 1, 3, 5, 7 and 9, the contribution will be the position on the scale minus 1. For points 2, 4, 6, 8 and 10, the contribution will be 5 minus the position on the scale. The sum of the results is multiplied by 2.5 to obtain the overall SUS value. The result will be between 0 and 100.

ANNEX IV. Instructions for the patient - Data Collection Guide

Hospital Universitario de Torrejón

LEGIT.HEALTH

LEGIT_COVIDX_EVCDAO_2022

Dra. Leticia Calzado

Servicio de Dermatología del
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Hospital Universitario de Torrejón

Instrucciones para el paciente

GUÍA DE RECOGIDA DE DATOS

Servicio de dermatología

Bienvenido/a,

El COVID-19 ha provocado en los hospitales una saturación de pacientes con esta patología que ha provocado en muchos casos la desatención de enfermedades dermatológicas. Debido a esto, es necesario la implantación de un sistema alternativo para que los pacientes dermatológicos puedan seguir siendo diagnosticados de sus respectivas patologías y también se les pueda realizar un seguimiento remoto y continuado de la enfermedad. Por ello, su médico le ha ofrecido la oportunidad de participar en este estudio, cuya finalidad es avanzar en nuestra comprensión de esta enfermedad y ayudar a los pacientes que la sufren.

¿Qué tiene que hacer durante el estudio?

Participar en este estudio consiste en informar de forma periódica sobre el estado de su patología. Es decir, deberá tomar nota del estado y evolución de su patología de forma periódica, sin que sea necesario que el médico esté con usted, proporcionándole mayor autonomía y comodidad.

Para ello, utilizará una herramienta digital (aplicación móvil) que le permitirá enviar fotografías de las zonas asignadas por su médico. Además, le permitirá rellenar cuestionarios que ayudarán a tener un registro de la evolución de su enfermedad.

¿Cómo debe informar del estado y evolución de su psoriasis?

Su médico le dará acceso a la **plataforma de Legit.Health,** a la que podrá acceder desde cualquier teléfono con acceso a internet.

¿Cómo se crea una cuenta en la plataforma?

Su médico le dará de alta en la plataforma mediante el correo electrónico que le indique y a continuación le llegará un email con la siguiente información:

Asunto: Dra. Leticia Calzado del Hospital Universitario de Torrejón ha creado una cuenta para usted en Legit.Health.

De: account@legit.health

Bienvenida/o,

Se ha creado una cuenta para usted en el Hospital Universitario de Torrejón. Sólo falta un paso: confirmar su cuenta.

Puede completar este paso haciendo clic en el botón:

Confirmar mi email

Tendrá que hacer click sobre el botón **Confirmar mi email** y aceptar los términos y condiciones legales para poder acceder a esta plataforma de dermatología digital.

La contraseña

La contraseña debe tener 8 caracteres, al menos una mayúscula, una minúscula, un número y un carácter especial, por ejemplo: uY74m%5Zb

¿Cómo se accede a la plataforma?

Si ya tiene creada la cuenta (es decir, si ha seguido los pasos del punto anterior), podrá acceder, desde cualquier dispositivo, a través del enlace **https://app.legit.health**.

Una vez en la ventana de inicio de sesión, introduzca su email y contraseña, y haga clic en **Confirmar**.

https://app.legit.health

Iniciar sesión

Por favor, introduzca sus credenciales de acceso

Email

miemail@gmail.com

Contraseña

uY74m%5Zb

Confirmar

Si tiene cualquier problema de carácter técnico, puede comunicarse con su médico en cualquiera de las visitas que tendrá con ella durante el estudio.

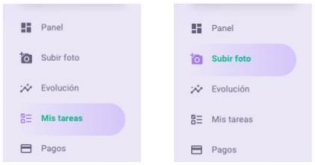
La aplicación no requiere descarga

Como puede ver, la aplicación no requiere descarga, sino que se accede desde el móvil u ordenador con navegadores como Chrome, Safari, Firefox o Internet Explorer en la dirección **https://app.legit.health.** También puede crear un acceso directo desde su navegador y añadirlo a su pantalla de inicio para tener un acceso más rápido y directo.

¿Cómo se rellena el cuestionario?

Una vez en la aplicación, podrá subir las fotografías y rellenar los cuestionarios a través de los siguientes botones, que encontrará tanto en el panel principal como en el menú de la izquierda:

1. **Botón Mis Tareas:** accederá al listado de tareas que debe realizar. Estas corresponden a cada una de las fotografías que debe subir a la aplicación, según las zonas y la frecuencia asignada en el estudio.
2. **Botón Subir foto**: accederá al inicio del proceso para subir la fotografía, que estará acompañado de instrucciones para facilitarle el uso.



¿Como se realiza el proceso para enviar información por la app?

En esta ventana, deberá seguir los pasos indicados:

1. Seleccione la zona del cuerpo que va a fotografiar.
2. Lea las instrucciones atentamente sobre cómo tomar la fotografía.
3. Suba la fotografía y recórtela, en caso necesario.
4. Responda a los cuestionarios que le aparezcan, según lo indicado en el protocolo.

A medida que vaya completando cada uno de los pasos del proceso, haga clic en **Siguiente**, hasta llegar a la última pantalla en la que deberá seleccionar el botón **Enviar** para finalizar. A partir de este momento, la información quedará registrada y su médico podrá realizar el seguimiento de forma telemática.

Adicionalmente al envío de fotografías para su médico, usted mismo podrá realizar un seguimiento de su patología, a través del apartado de **Evolución**. En esta sección podrá observar qué detecta el algoritmo, comparar imágenes y, en algunos casos, ver gráficas de evolución, que le ayudarán a tener mayor información sobre el estado de enfermedad.

¿Cuándo tendrá visitas con su médico?

Durante el periodo del estudio, acudirá a un total de **tres (3) visitas de revisión** con su médico.

Las visitas se realizarán al 1er mes, al 3er mes y al 6º mes desde la visita de inclusión en el estudio. Durante esas visitas, **su médico le podrá responder a las dudas que le hayan surgido** en relación al uso de la aplicación.

En la última visita (mes 6), su médico recogerá también un último cuestionario, llamado "Cuestionario de satisfacción para el paciente" y el Cuestionario de Usabilidad de la app.

¿Qué cuestionarios deberá rellenar a través de la aplicación?

1. De forma periódica, el paciente documentará el estado de su patología mediante los **cuestionarios correspondientes a cada patología** y el **DLQI**, los cuales están integrados en Legit.Health y se rellenan junto con la toma de la fotografía.
2. Al finalizar el estudio, el **Cuestionario de Satisfacción** y el **Cuestionario de Usabilidad de la app** para conocer cómo ha sido su experiencia.

ANNEX V. Dermatology Life Quality Index (DLQI - Dermatology Life Quality Index)

The purpose of this questionnaire is to evaluate to what extent your skin problems have influenced your life during the last 7 (seven) days. Please check one box for each question. Please check that you have answered ALL questions. Thank you.

Start time What time do you start filling out the questionnaire?	__ __ : __ __	example: 1 3 : 4 6

Please check one box for each question.

1. During the last seven days, have you had itching, pain or stinging of your skin?				
☐ Very much	☐ Much	☐ A little	☐ Not at all	

2. During the last seven days, have you felt embarrassed or self-conscious because of your skin problems?				
☐ Very much	☐ Much	☐ A little	☐ Not at all	☐ Not applicable

3. During the past seven days, have your skin problems interfered with shopping or taking care of the house or deck?				
☐ Very much	☐ Much	☐ A little	☐ Not at all	☐ Not applicable

4. During the last seven days, have your skin problems influenced the clothes you have worn?				
☐ Very much	☐ Much	☐ A little	☐ Not at all	☐ Not applicable

5. During the past seven days, have your skin problems affected any social or leisure activities?				
☐ Very much	☐ Much	☐ A little	☐ Not at all	☐ Not applicable

6. During the last seven days, has it been difficult for you to practice any sport because of your skin problems?				
☐ Very much	☐ Much	☐ A little	☐ Not at all	☐ Not applicable

7. During the past seven days, have your skin problems **prevented** you from working or studying?				
☐ Yes	☐ No			
If "No", during the last seven days, has your skin caused you any problems at work or school?				
☐ Very much	☐ Much	☐ A little	☐ Not at all	☐ Not applicable

8. During the last seven days, have your skin problems caused problems with your partner or a close friend or family member?				
☐ Very much	☐ Much	☐ A little	☐ Not at all	☐ Not applicable

9. During the past seven days, have your skin problems made your sex life difficult?				
☐ Very much	☐ Much	☐ A little	☐ Not at all	☐ Not applicable

10. During the last seven days, has the treatment of your skin been a problem for you, e.g., because it has made your home dirty or taken up your time?				
☐ Very much	☐ Much	☐ A little	☐ Not at all	☐ Not applicable

Questionnaire administration time: How long did it take you to answer the questions?	
Score:	

Thank you very much for your contribution.

ANNEX VI. Data collection notebook

Attached is an excel file with the variables to be collected

ANNEX VII. EC Declaration of Conformity

EC Declaration of Conformity document is attached