SEPD
SOCIEDAD ESPAÑOLA
DE PATOLOGIA DIGESTIVA

**Harmonizing diagnosis and therapy of Eosinophilic Esophagitis (EoE) across Europe (HaEoE-EU)**
UEG National Societies LINK Award Programme

in association with
UNITED EUROPEAN GASTROENTEROLOGY
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# ***European Registry of Clinical, Environmental and Genetic Determinants in Eosinophilic Esophagitis***

## **Organisation´s agreement (v.1b - 01/07/16)**

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**FUNDING:**

**INTERNATIONAL PROJECT PROMOTER:**

**United European Gastroenterology (UEG) – LINK Award Programme**

The UEG is an international, professional and non-profit organization that combines all major European scientific societies interested in Digestive Diseases. Together, the UEG member societies represent over 22,000 specialists, working in medicine, surgery, pediatrics, oncology and gastrointestinal endoscopy. Due this the UEG is the most comprehensive organization in its area in the world, and a unique platform for collaboration and knowledge sharing.

The **LinkAward** programme is promoted by the Committee of National Societies UEG to help in the funding of European projects coordinated by at least two National Societies, members of the UEG. The project's funds up to 100,000 euros to be invested in 1-2 year.

https://www.ueg.eu/awards-grants/ueg-awards/link-award/?no_cache=1

**LEAD ORGANIZING SOCIETY**

**Spanish Society of Digestive Diseases (SEPD, *Sociedad Española de Patología Digestiva*)**

The SEPD is a scientific and professional non-profit organization whose purpose is the promotion and dissemination of research and knowledge in the field of digestive diseases, basic, epidemiological, diagnostic and therapeutic, preventive and promotional health and promoting its practical application, providing value to both partners and patients and general population. It brings together more than 2,500 members.

The "**Harmonizing diagnosis and therapy of Eosinophilic oesophagitis (EoE) across Europe" (HaEoE-EU) project** has been granted in 2014 LinkAward call, beginning in November 2014, with an implementation period until December 2016. This agreement applies to the part of the project related with the patient's registry.

**INTRODUCTION AND BACKGROUND**

**Eosinophilic esophagitis (EoE)** is an inflammatory disorder determined by an immune response, which is chronic in nature, and defined from the clinical point of view by symptoms referred to esophageal dysfunction, and histologically by an inflammation of the esophagus with a predominance of eosinophils.

Despite the short history of EoE (it was first characterized as a specific clinicopathologic syndrome only 2 decades ago), this disease has been already recognized as the most common cause of chronic or recurrent esophageal symptoms after gastroesophageal reflux disease (GERD), and the leading cause of dysphagia in children and young adults in Europe and the countries of North America, with a prevalence of 45 to 55 cases per 100,000 inhabitants, according to several studies. Lately, it has also emerged as a disorder with increasing frequency in other regions, such as North Africa, Central and South America, and Asia. As a result, EoE now represents a chronic common health problem, which implies a significant impairment in the quality of life of patients suffering from it. Additionally, EoE represents a significant burden on the health care systems, as has already been estimated in the United States, where the care of patients with EoE represents a cost of up to 1,400 million dollars annually.

Since the initial descriptions of the disease in the early 1990s, EoE has been recognized as a particular form of food allergy, although its dietary management has presented a variable effectiveness according to the type of intervention. At the same time, a wide range of options to treat patients with EoE, from endoscopic dilations aimed at resolving esophageal strictures by enlarging the caliber of the esophagus, to different drugs, mainly including topic steroids, inhibitors of acid secretion, anti-allergic agents, and even monoclonal antibodies. In recent years, clinical research with high-quality designs, including randomized controlled trials (RCTs) and prospective studies, have evaluated the efficacy of the different treatment options available to achieve and maintain disease remission in patients with EoE. This has been recently summarized in several systematic reviews and meta-analyses in order to help doctors with evidence for decision-making on the complex management of this disorder.

However, the management of EoE remains complex, due to difficulties to combine individual aspects of each patient and health resources available in each of the clinical environments in which they are attended, the specific absence of specific drugs approved to be used in EoE, and the absence of solid data on the origin of the disorder, the factors that determine their prognosis, and personal and social costs involved in the clinical course of the disease.

For all these reasons, EoE currently represents a health and social challenge, which commits a considerable proportion of young patients, with a complex management that requires the collaboration of multiple specialists (gastroenterologists, allergists, pathologists, nutritionists, pediatricians, etc.) for a proper management of the disease.

But simultaneously, EoE also represent an extraordinary opportunity for research in the field of diseases with an immuno-allergic basis, which are in continued expansion in the countries of our environment.

For this reason, a group of European researchers and clinicians began designing an ambitious project in 2013, to settle in Europe the foundation for future clinical and epidemiological research on eosinophilic esophagitis. Synergies from their respective National Scientific Societies integrated into the United European Gastroenterology allowed the design of a common research project and its submission to the UEG Link Award program. This program promotes the establishment of links between European National Societies in the field of Gastroenterology, supporting them in promoting trans-national activities of scientific and professional cooperation.

The **HaEoE-EU project**, supported by 14 scientific societies, and led by the SEPD, was recognized by the UEG Link Award 2014 and its development promoted with funds from the UEG.

*The specific objectives of HaEoE-EU project include:*

[1] The construction of a European network to optimize the diagnosis and treatment of EoE by integrating allergists, pediatric and adult gastroenterologists, pathologists and ENT specialists, among others, in Europe.

[2] Developing and updating multidisciplinary European guidelines for the diagnosis and treatment of EoE patients. In particular, the development of new high-quality evidence-based clinical practice guidelines.

[3] Establishing a European registry of patients with EoE to improve our understanding on the epidemiology, trends in evolution, and the burden of disease for patients and health systems across Europe, and as a basis for the implementation of new collaborative prospective studies.

[4] To design and build a multilingual web platform to disseminate knowledge on EoE, as a reference resource to provide patients, caregivers and physicians high quality information and resources about the disease.

This project obtained the approval from the **Ethics Committee on Clinical Research** at the **Hospital Universitario de la Princesa (Madrid)** in september 2015. **It represents the development of point [3] of the project program Ha-EoE-EU (European registry of patients). The name of this part of the project is "EoE CONNECT".**

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## ***EoE Connect:***

## European Registry of Clinical, Environmental and Genetic Determinants in Eosinophilic Esophagitis

Although the aetiology of EoE is unknown, preliminary epidemiological, clinical and, recently, genetic analyses indicate that EoE, like other diseases with immuno-allergic basis, appears as the result of environmental factors acting over genetically predisposed individuals. The knowledge of the environmental factors that influence the development and course of the disease are currently quite limited, but their identification could pose the future development of preventive strategies.

Genetic factors play an important role in the pathogenesis of diseases of the immune system. Several observations supporting its role in EoE derive from the big differences in the incidence of EoE related to gender (being up to 4 times more common in males) in the different ethnic groups, the frequent familial aggregation of cases of EoE, and the greater concordance for EoE in monozygotic compared to dizygotic twins. The characterization of genetic factors contributing to the EoE has not been developed due to the relative youth of the disease, but it is certainly one of the most important issues to be discovered and to understood regarding the origin and evolving of this disease.

### TARGETS OF EoE CONNECT

### 1. General Approach

The overall objective of the project EoE CONNECT is the establishment of an infrastructure as well as its operating procedures necessary for the continued development of multicenter collaborative studies (including clinical, environmental, and epidemiological studies) about the different factors involved in the aetiology and pathophysiology of EoE.

### 2. Specific Objectives

1. To promote studies about the influence of environmental factors in the course of EoE.

2. To promote studies to phenotypically characterize patients with EoE.

3. To promote studies about the efficacy and safety of drugs used in EoE patients.

4. To promote epidemiological studies related to EoE.

5. To promote studies about the use of health resources in the care and assistance of EoE patients.

6. To disseminate scientific and technical knowledge through documentation and researcher’s meetings.

## PATIENTS

Patients will be included in the project if they have an established diagnosis of EoE. Signing an informed consent document is mandatory, after oral and written information has been provided by clinicians and researchers.

In the case of patients under 16 years of age, or adults who are not in a position to understand the project or signing the informed consent, due to lack of capacity, the consent of parents or legal guardians will be obtained. Upon reaching adulthood, minors must re-consent their participation in the EoE CONNECT project.

An exclusion criterion will be, therefore, patient's refusal to consent.

## GATHERING OF CLINICAL INFORMATION

Each centre, through an individual or a group of clinicians-researchers, will use a web-based registry to fill-in the clinical patient information considered relevant to the development of the studies foreseen or under development. This information will be regularly updated by clinicians-researchers who follow their patients.

Clinical information will be collected in electronic database forms specially designed for this project and stored in a unique and secure server in Spain (during the LinkAward project). The collection of information is limited to that essential and relevant for the purpose of the registry and the studies to be developed under EoE CONNECT.

In order to carry out some studies, EoE CONNECT information may be used for identification of cases for which clinical-researchers involved may seek additional information from each of the institutions involved in a particular study.

## IDENTIFICATION OF PATIENTS, CONFIDENTIALITY AND DATA STORAGE

In order to facilitate the collection of clinical information and to protect patient privacy, the information is collected under identification codes. Identification codes will be generated by the program database automatically within a pre-specified synthaxis approved by the Steering Committee.

Clinical information from each patient must include a tab with complete personal data of the patient (affiliation, etc.), which will interact with EoE CONNECT project code. Access to the relationship between personal data and the project code EoE CONNECT will only be accessible to the attending physician that created the information, so that he/she can identify the patient and communicate the results if deemed necessary by any reason, including the patient's will and the best treatment.

Clinicians-researchers will only have access to the codes with their corresponding clinical information associated. Maybe in the future, if properly implemented, clinical information could also be associated with biological samples for biobanking purposes, with coded DNA samples in the case of genetic studies.

## ACCESS TO CLINICAL INFORMATION

Clinical information of all patients will be collected in a common EoE CONNECT database project including: personal data of the patient, characteristics of their disease, associated allergic or immune diseases, relevant family history, explorations for the diagnosis of the disease, treatments received, respond to them and associated adverse effects, outpatient visits, complementary examinations and endoscopic and histological controls, and complications thereof.

Information on risk factors for developing the disease will also be collected, including family history, comorbidities and information on the descendants, history of environmental exposure during childhood and adolescence, and residential characteristics.

Participant clinicians-researchers (mostly specialists in gastroenterology or allergy) within a single centre will have full access to the information generated in the centre, including personal data of patients.

Clinicians-researchers responsible for a particular study will have access to patient information included in the particular study contained in the general database and properly coded, in which cases will only be identified by the EoE CONNECT code without personal data. Eventually, if required by the design of a particular study, an anonymized data exchange might be considered, although the nature and meaning of such records often lost much of its clinical-epidemiological anonymization utility.

## DISCLOSURE OF INFORMATION

The results of the research studies carried out using clinical and/or epidemiological project information can be made public in the form of presentations or scientific publications, usually as aggregated data. The information derived from a specific sample will never be disclosed, and at all times the maximum anonymity of the data is guaranteed.

Publications resulting from the clinical information (and if implemented in the future, with associated biological samples in a biobank, with potential use of genetic material) of the EoE CONNECT project will recognize the authorship of researchers who have contributed in a significant way to the design, conducting and analysis of the study, as well as contributors who have produced a significant amount of clinical and epidemiological information. To determine authorship, the rules recommended by the International Committee of Biomedical Journal Editors will be followed. In all cases it will be recognized in the publications that the work has been done in the environment of the EoE CONNECT project and Ha-EoE-EU LinkAward project.

## PROJECTS DEVELOPED FROM THE INFORMATION ENTERED IN EoE CONNECT

The EoE CONNECT project will develop operating policies and protocols, generating patient records, management and ownership of local files of participating health centres, data transfer protocols for sharing encrypted files, management and ownership of European files with the encoded data transferred, which will include:

1. Project management and scientific studies
2. Use of recorded data
3. Process for proposal and presentation of studies
4. Policy for authoring in projects supported in the database Ha-EoE-EU.

## ECONOMIC ISSUES

The HaEoE-EU project is an altruistic collaboration of researchers and their national scientific societies, and does not pursue profit. Researchers do not receive financial compensation for their work, and funds are fully allocated to the achievement of the objectives of the program. The UEG has established a protocol for monitoring the program, with periodic technical, scientific and financial reports.

EoE CONNECT is part of UEG-SEPD Ha-EoE-EU Link Award program, and has a specific budget for its development (as objective 3 – Patient Registry)

## DISCLAIMER

The EoE-CONNECT project has been built around a European network of researchers involved in EoE as a result of the Ha-EoE-EU UEG Link Award project, coordinated by the SEPD (Spanish Society of Digestive Diseases) and with more than a dozen of National Scientific Societies integrated in the UEG taking part, as well as other associations, with special relevance of the European Society of Eosinophilic Esophagitis (EUREOS) (www.eureos.online).

The National Society's coordinator, the Spanish Society of Digestive Diseases (SEPD) assumes the representation of this project to completion and final justification with the UEG by January 2017. After this date, it's up to participating National Societies and/or Association of EoE researchers or European organizations interested in this field to agree upon future conditions for its long term sustainability, the final goal of this effort.

The management of the server where the integrated clinical information is stored has been contracted with Atentis Business Solutions, SL, established in Avda. De Europa, 2, 28224 Pozuelo de Alarcón (Madrid, Spain) and with CIF B83850818.

System information processing will be through a central server with remote internet connection type.

High level security measures shall be adopted for the treatment of clinical information as required by law (national and European).

The body in charge of integrated data processing will be the SEPD, through their own means or those who once contracted. Transfer of any encoded data of the integrated database for a specific study within the project's aims, will be agreed by the appropriate legal document complying with the relevant national and European legislation. The SEPD will be responsible for the integrated database and data processing until the completion of the project. Subsequent assignments can be performed, through integrated national members on this platform. In the event that the integrated database could hold any personal data that must be protected by the application of the legislation data protection, the SEPD will be responsible for registering the database integrated in the protection agency data and comply with all regulatory provisions in force. In this case, any particular patient may exercise the rights of opposition, access, correction and cancellation in the corresponding health centre.

There will be no public access to the data.

The establishment and management of this project is free of any commercial benefit.

## ADDITIONAL CLARIFICATIONS

This phase of the project involves the creation of a network infrastructure and operating procedures for registering cases of EoE diagnosed in European countries, with their clinical, epidemiological and follow-up information, not including now the storage of biological samples for genetic analysis. Therefore, it has not seen the availability of liability insurance for medical interventions beyond obtaining informed consent, the absence of risk invasive procedures for participating patients.

The EoE CONNECT registry intends to be, in the medium term, the international reference source for epidemiological studies in EoE, and might be implemented in the future associating a **biobank** with possible genetic DNA analysis. **This implementation will require a new development which should obtain specific funding in new research calls.**

The cited implementation of a biobank with DNA analysis of biological samples for this project will require a specifically designed protocol, which will consider issues related to the treatment of biological samples and obtaining genetic material, watching the coverage of the legal and ethical responsibilities that would in that case be considered. **In the current stage of development of the project** and while no specific approval is submitted for these purposes, **the research team agrees not to make any extraction of biological information under the consent and participation in the registry hereby presented.**

SIGNATURES AND DATES

For the SEPD (project Coordination)

Dr. Alfredo José Lucendo Villarín
HaEoE-EU Coordinator Project

Madrid, 1st July 2016

For the PARTICIPANT CENTER

Name Center ____________________________________

Unit/Department _________________________________

City (Country) ___________________________________

*Clinician-Researcher*

Dr.
(Position)

*Head of the Unit/Department (if needed)*

Dr.
(Position)

*Director of the Hospital/Center (if needed)*

Dr.
(Position)

Date, place: _____________________________________

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