ORIGINAL ARTICLE

Protocol of the European Registry on the management of *Helicobacter pylori* infection (Hp-EuReg)

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As Scientific Committee of the Hp-Eureg on Behalf of the National Coordinators*

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Abstract

Introduction: *Helicobacter pylori* selectively infects the human stomach, being the most prevalent chronic infection in the world. *H pylori* presence causes chronic gastritis in 100% of infected patients and is the major cause of relevant diseases such as atrophic gastritis, peptic ulcer disease, and gastric cancer; it is for this reason that from a public health standpoint, it is considered a high-impact pathogen, responsible of a significant morbidity and mortality. Nowadays, there are consensus and clinical guidelines regarding the infection management at a European level and in most of European countries, but no data have shown the level of implementation of these recommendations. The high costs that this infection carries both socially and to the health system require the continuous and systematic assessment of the diagnostic and treatment strategies, as well as the accessibility to diagnostic methods and most efficient drugs.

Aim: To register the diagnosis, management strategies, and treatment of *H pylori*-infected adult patients in the Digestive Services outpatient clinics throughout Europe.

Methods: Noninterventionist prospective multicentre international Registry promoted by the *European Helicobacter and Microbiota Study Group*. National Coordinators will select recruiting gastroenterologists in their country that will register the *H pylori*-related routine clinical practice consultations they receive in an electronic case report form (e-CRF) provided by AEG-REDCap. Variables retrieved will include clinical, diagnostic, treatment, eradication confirmation, and outcome data. The database will allow researchers to perform specific subanalyses after approval by the Scientific Committee of the study.

KEYWORDS
antibiotics, clinical practice, *Helicobacter pylori*, implementation, recommendations, Registry

1 | INTRODUCTION

Helicobacter pylori presence causes chronic gastritis in 100% of infected patients and is the major cause of relevant diseases such as

atrophic gastritis, peptic ulcer disease, and gastric cancer.[1,2] *H pylori* eradication prevents peptic ulcer recurrence and its complications and decreases the incidence of gastric cancer. Furthermore, *H pylori* eradication in patients with peptic ulcer or even functional or noninvestigated dyspepsia is a cost-effective strategy.[3-5]

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*List of National Coordinators is included as Appendix S1.

The most common clinical manifestation of *H pylori* infection is dyspepsia, a major health problem, whose prevalence reaches more than 10% among adult populations with its attendant burden of morbidity and health system costs in diagnosis and treatment.[6] Approximately 20% to 30% of people in the community each year report chronic or recurrent dyspeptic symptoms, and consultations for dyspepsia account for up to 40% of referrals among gastroenterology outpatients, the *H pylori* "test-and-treat" strategy being the most cost-effective.[7-10] Moreover, *H pylori* is the major cause of peptic ulcer disease, causing over 90% of duodenal and 70% of gastric ulcers.[11-14] Considerable evidence supports that the nature of the chronic inflammatory process driven by *H pylori* is of critical importance in gastric carcinogenesis (adenocarcinoma and mucosa-associated lymphoid tissue –MALT– lymphoma).[2,15] It is for that reason that the WHO's International Agency for Research on Cancer classified *H pylori* as a group 1 (definite) carcinogen.[1,16]

Scientific evidence demonstrates that diagnosis and eradication of *H pylori* are the most cost-effective strategy in the management of dyspepsia, peptic ulcer, and gastric cancer prevention.[3] The treatment regimens are very diverse and have changed overtime. Monotherapies and treatments with two drugs did not achieve acceptable eradication rates. The commonly recommended regimen in most consensus conferences is the standard triple regimen, combining two antibiotics (clarithromycin with amoxicillin or metronidazole) and a proton-pump inhibitor (PPI) for 7 to 14 days. Another recommended alternative is bismuth-containing quadruple therapy (PPI, tetracycline, metronidazole, and bismuth salts). In the last years, results with new and efficient rescue regimens including levofloxacin have been published. Lately, new treatments have been proposed, including nonbismuth quadruple regimens, with two main variants: the "sequential" treatment (an induction phase with PPI and amoxicillin and a second phase with PPI, clarithromycin, and metronidazole) and the "concomitant" treatment (same four drugs taken altogether).[3,4,17-21]

The great diversity of regimens and treatment lines, the different efficacy of these, mostly due to the increase in bacterial antibiotic resistance and regional differences, requires a continuous critical analysis of clinical practice, evaluating systematically the efficacy and safety of the different regimens and the cost-effectiveness of the different diagnostic-therapeutic strategies.[22,23] This will help in the design of an efficient and optimized treatment that will reduce number of re-treatments, diagnostic tests, and the appearance of associated pathologies such as peptic ulcers and, probably, gastric cancers. Therefore, the evaluation of real clinical practice using noninterventionist registries will help to improve the design and organization of European Consensus on the management of *H pylori* infection, which is the best way to establish healthcare efficiency.[22,24-26]

It is hard to decide which treatment will provide good results (≥90% cure rates) aligned with current recommendations and standards.[27] Evidence from clinical trials may be equivocal because it is impossible to perform a single randomized trial to evaluate all these treatments. Network meta-analyses, however, may provide an acceptable pooled approach enabling combinations of data from several treatment trials to be analyzed.[28-30] However, evidence derived from clinical trials may not be extrapolated to clinical practice, in which there are no restrictive inclusion criteria, and where available care time per patient, and patient follow-up is more limited.[29]

Finally, there generally exists a delay from publication of recommendations to implementation of them in routine clinical practice,[31,32] sometimes reaching full penetration after being outdated.[33] Implementation scientists recommend therefore long-term studies evaluating practice and outcome trends, and tools able to provide real-time data from real practice (local, regional, and global).[34]

Therefore, the primary aim of the present Registry is to obtain a database registering systematically a large and representative sample of routine clinical practice of European gastroenterologists in order to produce descriptive studies of the management of *H pylori* infection. As secondary objectives, we aim to (a) evaluate *H pylori* infection consensus and clinical guidelines implementation in different countries; (b) perform studies focused on epidemiology, efficacy, and safety of the commonly used treatments to eradicate *H pylori*; (c) evaluate accessibility to healthcare technologies and drugs used in the management of *H pylori* infection; and (d) allow the development of partial and specific analyses by the participating researchers after approval by the Registry's Scientific Committee.

2 | METHODS

2.1 | Design

International multicenter prospective noninterventionist Registry promoted by the *European Helicobacter and Microbiota Study Group* (EHMSG; www.helicobacter.org).

2.2 | Research team

The Registry's research team is formed by the Scientific Committee, the Central Management Office, the National Coordinators, and the recruiting investigators.

The Scientific Committee is a collegiate interdisciplinary board of *H pylori* clinical research experts elected by the EHMSG in charge of the strategic decisions and the approval of the investigators, analyses, and manuscripts. The members of this board are Javier P. Gisbert acting as Principal Investigator, Francis Megraud, Colm A. O'Morain, and Adrian G. McNicholl acting as Scientific Secretary of the Committee and coordinator of the Central Management Office. The Scientific Committee conceived the project's idea and aims, approved the project protocol, and selected the Central Management Office.

The Central Management Office is comprised by scientific and management hired staff and is in charge of the coordination, monitoring, and analysis of the project at Hospital Universitario de La Princesa (Madrid, Spain). The office designed the study methodology and drafted the protocol for Ethic's approval.

In each country, a National Coordinator was invited based on its clinical and research activity. The National Coordinators constitute

the monitoring and drafting advisory board of the Registry. The National Coordinators are in charge of selecting recruiting investigators in each country and are responsible for the follow-up and quality of the recruiting, and the national and local legal compliances; they are the link between promoters and recruiting investigators. National Coordinators may analyze and publish their national data after approval by the Scientific Committee. The list of National Coordinators is included as Appendix S1: National Coordinators. Countries with compromised viability or lack of response/participation were excluded. Final included countries are shown in Figure 1: Map of participant countries.

The recruiting investigators must be gastroenterologists attending an adult population with a gastroenterology outpatient clinic that assists *H pylori*-infected patients. Clinicians regardless of their scientific background were asked to perform a feasibility selection process. This process included a questionnaire regarding, affiliation, contact details, outpatient clinic requisites, and potential conflict of interest. Before acceptance, the outpatient clinic must attend, in a clinical routine basis, patients in which *H pylori* diagnosis or treatment is indicated. Diagnosis and eradication confirmation tests have to be available. Recruiting investigators include patients and register them as cases in the project's database through an electronic case report form (e-CRF).

2.3 | Electronic case report form (e-CRF)

Study data are collected and managed using REDCap Electronic Data Capture tools hosted at "Asociación Española de Gastroenterología" (AEG; www.aegastro.es; [35,36] AEG is a nonprofit scientific and medical society focused on gastroenterology, and it provided this service free of charge, with the sole aim of promoting independent investigator-driven research. REDCap (Research Electronic Data Capture) is a secure, web-based application designed to support data capture for research studies, providing (a) an intuitive interface for validated data entry; (b) audit trails for tracking data manipulation and export procedures; (c) automated

export procedures for seamless data downloads to common statistical packages; and (d) procedures for importing data from external sources. A printout version of this e-CRF is included as Appendix S2: Printout e-CRF.

2.4 | Variables and outcomes

The e-CRF registers 290 variables including demographics, history and comorbidity, data on infection and diagnosis, previous eradication attempts, current treatment, compliance, adverse events, and efficacy. All personal data were anonymized. The main outcome is eradication of *H pylori* confirmed at least 4 weeks after treatment using locally accepted/validated diagnostic methods. Compliance is defined as having taken at least 90% of the prescribed drugs. Adverse events and compliance will be evaluated through patient interrogation with both open-end questions and a predefined questionnaire. Structure of the database and protocol flowchart is shown in Figure 2: Project Structure.

The intention-to-treat (ITT) analysis includes all registered patients up to 12 months before data extraction to allow for patients to finish procedures; lost to follow-up cases will be considered treatment failures. Per-protocol analysis includes all cases that finish follow-up and take at least 90% of the treatment drugs. A modified ITT will be used aiming to reach the closest result to those obtained in clinical practice. This modified ITT will include for analyses all cases with complete follow-up, not assuming any result after a 6-month follow-up on those without confirmatory test.

2.5 | Statistical analyses

Continuous variables will be presented as the arithmetic mean and respective standard deviation. Qualitative variables will be presented as percentages and 95% confidence intervals (95% CI).

Significance will be considered at $P < 0.05$. Multivariate analyses will be performed using a logistic regression model using the stepwise forward likelihood method with *H pylori*-modified ITT eradication as dependent variable and including age, gender, penicillin allergy, treatment duration, prior treatments, type and dose of PPI, compliance, center/region, and the currently prescribed regimen as independent factors.

A cluster analysis will performed to establish coherent regions for analysis and comparison based on geographic centroid distances of countries; boundaries between regions will be set based on internal gross product (IGP) per capita per year. Regions will be used to subanalyze results. A time trend analysis based on the year treatment was prescribed to the patient will be used to evaluate prescription use and efficacy trends.

2.6 | Ethics

The Hp-EuReg protocol was approved by the Ethics Committee of La Princesa University Hospital (Madrid, Spain) that acted as reference Institutional Review Board, was classified by the Spanish Drug
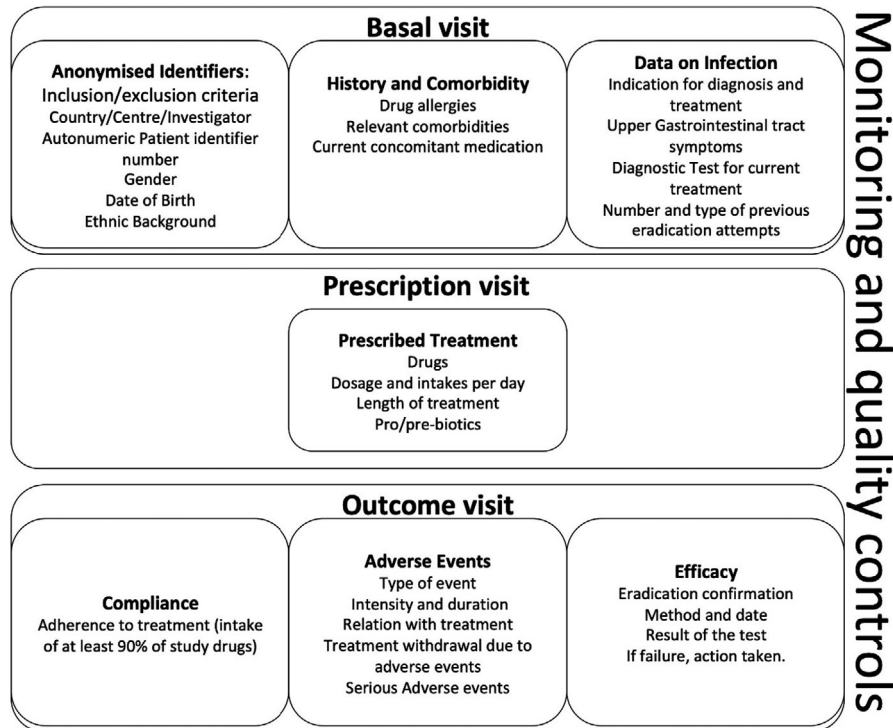

FIGURE 1 Map of participant countries

FIGURE 2 Project Structure

and Health Product Agency, and was prospectively registered at ClinicalTrials.gov under the code NCT02328131. An addendum for a ten-year extension of the project was also approved. Protocol approvals are included as Appendix S3: Ethics Approval.

3 | EXPECTED IMPACT OF RESULTS

The current project will allow constant real-time evaluation of *H pylori* management in clinical practice in a representative set of participant centers throughout Europe, the level of implementation of new recommendations derived from the published evidence and consensus conferences, the speed these improved practices are incorporated, and the effect on clinical outcomes.

After the publication of the IV European Consensus Conference on *H pylori* infection,[18] the EHMSG organized "The European Registry on the Management of *H pylori* infection" (Hp-EuReg) aiming to evaluate the real clinical practice of European gastroenterologists regarding the decision-making process (diagnosis, treatment, and follow-up) of *H pylori* infection. This project is allowing the medical-scientific community to improve future recommendations based not only on the evidence obtained from controlled clinical trials but also on the singularities of real day-to-day clinical practice in Europe.[26,29,37]

Across the different medical fields, there are very few studies evaluating the implementation of recommendations derived from consensus conferences and guidelines.[34] Moreover, the published studies tend to be local evaluations that cannot be extrapolated to large geographic areas with, not only differences on population

characteristics, but also differential accesses to diagnostic methods, treatment regimens, and with a wide variety of legislations and approaches regarding health care.[32,37-39] In this context, the utility of evidence-based recommendations is sometimes reduced as they become locally inapplicable and in some cases just purely theoretical.[31,34]

The EHMSG realizes that *H pylori* infection is a burden of paramount importance for the healthcare systems throughout Europe and the world as it affects over half of the world's population, and it is the leading cause of peptic ulcer and gastric cancer. However, there is an immense variety of strategies regarding the management of this chronic infection, affecting the indication, diagnosis, treatment, and follow-up.[25,40] Although the Maastricht IV and V Consensus provide clear recommendations, their implementation is not certain and, therefore, their effect for society is unknown.

The EHMSG acknowledges the value and utility of consensus conferences and evidence-based medicine and believes that *H pylori* infection can be successfully treated and eradicated if these recommendations are correctly followed.[41-44] However, the EHMSG also recognizes that the applicability of these recommendations needs to be continuously evaluated and that they should try to address the reality of clinical practice. In order to promote this new "applicability approach" and to measure the state of *H pylori* management in Europe, the main *H pylori* experts from Europe have been involved and will be coordinating the approximately 300 physicians (gastroenterologists) who have confirmed their participation in the Registry. Participants in the Hp-EuReg will be registering over 10 years all their clinical practice regarding the diagnosis, treatment, and follow-up of this infection. The

EHMSG expects to obtain the largest clinical database ever done on *H pylori*.

The analyses of this study will cover from rates of implementation of Consensus to outcomes analysis including number, type, manner and result of diagnosis, treatments, and management strategies. Global and local analyses will be performed trying to evaluate the data from all perspectives: medical, scientific, economic, and social. The Registry is more than just the procedure described in the protocol; it is a new approach to evidence-based medicine combining inductive and deductive rationalities. The Registry is the first step toward the elaboration of locally applicable recommendations from the overlap of trial evidence and practitioner experience.

The results from the Hp-EuReg will mean valuable data for future consensus conferences and guidelines, and information to health authorities and medical societies useful in the preparation of policies and actions to benefit the health assistance to their populations.

DISCLOSURES OF INTERESTS

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.