I.R.C.C.S. Ospedale San Raffaele

CLINICAL STUDY PROTOCOL

Study Code: PREM

Title: PRospective registry of Esophageal Motility

Principal Investigator: Dr. Barchi Alberto

CLINICAL STUDY PROTOCOL

***Title**: PRospective registry of Esophageal Motility*

Study Identifier	PREM
RSO number	NA
Other Protocol Codes	NA
Version	Ver 1.1
Date	12-02-2026

Sponsor	IRCCS San Raffaele Hospital
Co-Sponsor	NA
Authorized Sponsor Representative	Prof. Silvio Danese U.O. Gastroenterology and Gastrointestinal Endoscopy
Authorized Co-Sponsor Representative	NA
Funding Source(s)	NA
Principal Investigator	Dr. Barchi Alberto Esophageal Motility and Eosinophilic GI disorders Unit, U.O. Gastroenterology and Gastrointestinal Endoscopy, San Raffaele Hospital

VERSION HISTORY

Protocol version n.	Reason of changes	Date issued
1.0	*First Version submitted to the Ethics Committee (EC)*	*12-11-2025*
1.1	*Integrations to EC*	*12-02-2026*

PROTOCOL SIGNATURE PAGE

Study Title: *"PRospective registry of Esophageal Motility"*
Study Identifier: PREM

Protocol Version and Date: Ver 1.1 12-02-2026

The undersigned has read and understood all the aspects of the protocol detailed within this document and agrees to supervise and conduct the study in accordance with the protocol, the

Declaration of Helsinki, Guideline for Good Clinical Practice ICH E6 (R2), and all applicable regulatory requirements.

Silvio Danese, Prof.		U.O. Gastroenterology and Gastrointestinal Endoscopy, IRCCS San Raffaele Hospital	October 14TH , 2025
Authorized Sponsor Representative Name	**Signature**	**Affiliation**	**Date**

Dr. Barchi Alberto		U.O. Gastroenterology and Gastrointestinal Endoscopy, IRCCS San Raffaele Hospital	October 14TH, 2025
Principal Investigator Name	**Signature**	**Affiliation**	**Date**

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1. KEY STUDY CONTACTS

Sponsor	Ospedale San Raffaele Via Olgettina, 60 20132 – Milano, Italy
Co-Sponsor	NA
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Authorized Co-Sponsor Representative	NA
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Funding source(s)	NA
Clinical Trial Center	Email: ctc.firstcontact@hsr.it; ctc.trialstartup@hsr.it; ctc.datamanagement@hsr.it; ctc.quality@hsr.it

2. SYNOPSIS

Study Identifier	PREM
Study Title	PRospective registry of Esophageal Motility
Protocol Version and Date	Vers 1.1 12/02/2026

Sponsor	IRCCS Ospedale San Raffaele	
Co-Sponsor	NA	
Funding Source(s)	NA	
Principal Investigator	Dr. Alberto Barchi	
Study Description	PRospective registry of Esophageal Motility	
Study Design	Prospective	
Primary Objective To register clinical, endoscopic, physiologic, radiographic data on patients referred for esophageal motility/inflammatory disorders or reflux/obstructive esophageal symptoms at San Raffaele Hospital	**Primary Endpoint** NA	**Time point(s)** NA
Secondary Objectives NA	**Secondary Endpoints** NA	**Time point(s)** NA
Exploratory Objectives NA	**Other** NA	**Time point(s)** NA
Study Population	Patients with reflux (typical or atypical) or obstructive esophageal symptoms on or off therapy, Barrett Esophagus patients, pts with eosinophilic esophagitis, gastroparesis, patients with primary motility esophageal disorders, patients undergone to foregut GI surgery procedures (esophageal myotomies, anti-reflux surgeries, bariatric procedures, gastroparesis surgery), Age > 18 years	
Inclusion Criteria	Age > 18 years, Patients with reflux (typical or atypical) or obstructive esophageal symptoms on or off therapy, Barrett Esophagus patients, pts with eosinophilic esophagitis, gastroparesis, patients with primary motility esophageal disorders, patients undergone to foregut GI	

	surgery procedures (esophageal myotomies, anti-reflux surgeries, bariatric procedures, gastroparesis surgery), Age > 18 years
Exclusion Criteria	Age < 18 years
STUDY OBJECT: integrating and analyzing physiopathologic outcomes with clinical, demographic, endoscopic and radiographic data	
DRUG: No specific drug is evaluated in this protocol, aside the clinical practice	
Additional procedure	NA
MEDICAL DEVICE: NA	
PROCEDURE: NA	
Sample Size	Every patients reaching out Digestive Physiopathology division of Gastroenterology and Digestive Endoscopy of San Raffaele Hospital
Statistical Design	NA
Duration of the Study	Duration of enrollment: 5 years Duration of subject participation: 10 years Duration of total study period: 15years

3. ABBREVIATIONS AND DEFINITIONS

3.1. Abbreviations

CIOMS	Council for International Organization of Medical Science
CRF	Case Report Form
CRO	Contract Research Organization
CTC	Clinical Trial Center
DPIA	Data Protection Impact Assessment
EC	Ethics Committee
GCP	Good Clinical Practice
ICF	Informed Consent Form
ICH	International Conference on Harmonization
LVLP	Last Visit of Last Patient
MedDRA	Medical Dictionary for Regulatory Activities
OSR	Ospedale San Raffaele
PI	Principal Investigator
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
EoE	Eosinophilic Esophagitis

3.2. Definitions

4. BACKGROUND AND RATIONALE

Digestive physiopathology is a branch of gastroenterology aiming to study patients with upper GI symptoms, mainly gastro-esophageal, potentially indicating the presence of Gastroesophageal Reflux Disease (GERD)/Barrett Esophagus (BE) or obstructive esophageal motility disorders (achalasia being the most relevant), but including also other primary motility disorders such as Esophgago-Gastric Junction Outflow Obstruction (EGJOO), Hypercontractile Esophagus (HE), Distal Esophageal Spasm (DES) and other minor disorders. Physiopathological testing encompasses High-Resolution Manometry (HRM), 24-H esophageal pH-impedance testing, Functional Lumen Imaging Probe (FLIP) assessment. All these tests are designed to provide a clear phenotyping of esophago-gastric disorders related to reflux or obstructive esophageal symptoms, either in naïve patients, as well as after foregut surgery (particularly anti-reflux surgery, achalasia/primary motility disorders treatment).

5. OBJECTIVES AND ENDPOINTS

Primary objective of the study is to create a prospective/retrospective registry of all patients with > 18 years of age referring to the Digestive Physiopathology division of San Raffaele Hospital, in order to register clinical, endoscopic, radiologic data of these patients integrating them with physiopatology outcomes in order to shape disease management and treatment work-up, also in long-term follow-up of these patients.
Primary endpoints are the Integration and analysis of association/correlation of physiologic with endoscopic, radiologic and clinical data.

Objectives	**Endpoints**	**Time point(s)**
Primary Objective To register clinical, endoscopic, physiologic, radiographic data on patients referred for esophageal motility/inflammatory disorders or reflux/obstructive esophageal symptoms at San Raffaele Hospital	**Primary Endpoint** NA	**Time point(s)** NA
Secondary Objectives *NA*	**Secondary Endpoints** *NA*	*NA*
Exploratory Objectives *NA*	**Other** *NA*	*NA*

6. STUDY DESIGN

PREM is a prospective registry recruiting patients retrospectively enrolled aiming to include all clinical, endoscopic, radiological integrating them with physiopathology data of all patients referred to Digestive Physiopathology Division of San Raffaele Hospital, with the purpose of extracting data for prospective and retrospective analyses, in order to improve patients' management and clinical research and empower diagnostic and therapeutic work-up

Commentato [RT1]: Specificare che saranno inclusi solo pazienti arruolati retrospettivamente

6.1. Study duration

Duration of enrollment: 5 years
Duration of treatment: 10 years
Duration of total follow-up: 10 years
Duration of total study period: 15 years

7. STUDY POPULATION

7.1. Study Participants

Patients with reflux (typical or atypical) or obstructive esophageal symptoms on or off therapy, Barrett Esophagus patients, pts with eosinophilic esophagitis, gastroparesis, patients with primary motility esophageal disorders, patients undergone to foregut GI surgery procedures (esophageal myotomies, anti-reflux surgeries, bariatric procedures, gastroparesis surgery), Age > 18 years

7.2. Inclusion Criteria

Inclusion criteria to be included in the registry are:

1. Participant is willing and able to give informed consent for participation in the study.
2. The procedures are the standard of care for the patient or the participant is taking the medicinal product according to clinical practice
3. Aged > 18 years.
4. Any typical (heartburn or regurgitation) or atypical reflux symptom (Laryngeal Cough, laryngitis, sub-glottic stenosis, globus, laryngeal cancer, vocal cord granuloma, vocal cord irritation, vocal cord polyps and post-nasal drip; Oropharyngeal: Dental erosion, pharyngitis, sore or burning throat, gingivitis and halitosis; Ears and sinuses: Earaches, otitis media and sinusitis; Pulmonary: Chronic bronchitis, pneumonia, aspiration, bronchiectasis, asthma and idiopathic pulmonary fibrosis; Cardiac: Arrhythmia, angina and myocardial infarction; Sleep: Sleep apnoea, sleep deprivation, insomnia, snoring, nightmare and sleep disturbance), but also any obstructive esophageal symptom potentially reflecting a primary

or secondary motility disorder (oropharyngeal or esophageal dysphagia, chest pain, bolus impaction). Every patient with a diagnosis of esophageal inflammatory disorder (including EoE and others) or systemic rheumatological condition (scleroderma, systemic sclerosis, lichen planus and others), every patient previously undergone to any anti-reflux surgery, bariatric surgery, endoscopic or surgical esophageal or gastric myotomy (also for gastroparesis) may be included.

5. Patients must be referred to the Digestive Physiopathology Unit of IRCCS San Raffaele Hospital for motility tests

7.3. Exclusion Criteria

1. Age < 18 years
2. Not willing to provide informed consent to the inclusion in the registry

7.4. Screening Failures

NA

8. STUDY OBJECT

Integrating and analyzing physiopathologic outcomes with clinical, demographic, endoscopic and radiographic data registry

8.1. Study object description

NA

9. STUDY PROCEDURES

	Enrollment	**Follow-Up Visits**
Procedures **Day**	*T0*	*T1 (if available)*
Informed consent	X	X
Demographics	X	X
Medical history	X	X
Eligibility assessment	X	X
Physical examination (including height and weight)	X	X
Radiologic/Imaging assessment	x	x
Digestive Physiopathology tests	x	x
Questionnaires (GERDQ, GERD-HRQL, RSI,ECKARDT, BED-Q, GSS)	x	x

9.1. Informed Consent

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be EC-approved, and the participant will be asked to read and review the document. The investigator (according to applicable regulatory requirements) or a person designated by the investigator, and under the investigator's responsibility, will explain the research study to the participant and answer any questions that may arise. A verbal explanation will be provided in terms suited to the participant's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Participants will have the opportunity to carefully review the written consent form and ask questions prior to signing. The participants should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The participant MUST sign the informed consent document prior to any procedures being done specifically for the study/any data is collected. Participants must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to the participants for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedure/ any data is collected. The rights and welfare of the participants will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

9.2. Subject Recruitment and Screening

Every patient as per clinical routine in our hospital will undergo a general outpatient consultation before the physiopathology tests and procedures, with eligibility criteria screening for the enrollment in the registry and the signature of the IC.

9.3. Subject Identification

Starting from the signature of the informed consent by the patient or patient's legal tutor, the subjects is considered enrolled in the clinical study.
A subject identification code will be assigned consecutively (i.e.: PREM_HSR_001)

9.4. Baseline Assessments

Baseline assessment is made during an outpatient consultation as per clinical routine and international guidelines with the collection of demographics, clinical, radiologic, endoscopic data and previous details on medical and treatment history, and of course overall assessment of the indication for the physiopathology procedures. Clinical questionnaires used are already used in clinical practice.

Commentato [RT2]: Specificare che verranno eseguiti I questionari e che gli stessi sono già utilizzati da pratica clinica e inserire nella bibliografia la relativa validazione in italiano.

Commentato [AB3R2]: Già inserite le relative bibliografie più avanti

9.5. Visits and Follow Up

Follow-up visits and other follow-up physiopathology procedures could be undertaken if deemed necessary according to clinical decision-making. Therefore every patient is expected to attend the T0 assessment, while follow-up is optional.

9.6. Definition of End of Study

The study will end at the end of the last patient's follow-up period

9.7. Premature termination or suspension of a study

NA

10. DISCONTINUATION AND WITHDRAWAL

Participants are free to withdraw from participation in the study at any time upon request.
The reason for participant discontinuation or withdrawal from the study will be recorded on the clinical records and in Case Report Form (CRF). Subjects who sign the informed consent form and subsequently withdraw, or are withdrawn or discontinued from the study, will not be replaced.

11. SAMPLE HANDLING

NA

12. PATIENT SAFETY

NA

13. DATA MANAGEMENT

Not performed by a CRO

13.1. Definition of source data and source documents

All parameters asked for in the case report form (CRF) should be documented in the source documents.

13.2. Documentation of data in Case Report Forms (CRFs)

All relevant data collected during the study for all of the patients enrolled in the study shall be entered in the CRF by the principal investigator or someone authorized by the investigator in a timely manner (as soon as possible after the information is collected) to ensure that they are

clear and legible. The physician shall confirm the completeness, correctness, plausibility, and compliance with the ICH guidelines and the institutional SOPs of the data by dated signature. An explanation must be provided for any and all missing data. The entries shall be made with black ballpoint pen.
The properly filled in CRF will remain in the study site.
For the study will be used an eCRF (REDcap) and a copy of all pages will be conserved in the study site.
REDcap is a clinical electronic data capture system specifically developed around HIPAA-Security guidelines; more information on the consortium and system security is available at https.//www.projectredcap.org/.

13.3.Data Recording and Record Keeping

The investigator shall arrange for the retention of Essential Documents for the Conduct of a Clinical study (e.g., patient files, other source data, and the Trial Master File/Investigator Site File) after the completion or discontinuation of the study according to institutional procedures and applicable laws.

13.4. Data Protection

The Investigator (or the Center that will receive the data) undertakes to:
- use the data only for the purposes of the foreseen analyses and within the limits established by the study and approved by the competent EC;
- store data in a secure network system;
- prohibit unauthorised third parties from accessing, even partially, data.
- guarantees to limit access to and processing of data only to its employees and collaborators who, upon appointment as an authorized person:
  1. need to process the data in order to carry out their work in relation to the study;
  2. have undertaken to maintain the confidentiality of the Data and of any information deriving from it or that is communicated to them.

14. STATISTICS

NA

14.1. Description of Statistical Methods

NA

14.2. Sample Size Determination

NA

14.3. Analysis Populations

NA

14.4 Statistical Design

No statistical design needed. No sample size calculation was needed since the prospective registry nature of the study but nonetheless 10,000 patients will be enrolled

15. ETHICAL AND REGULATORY CONSIDERATIONS

This clinical study will be conducted in accordance with the principles laid down by the 18th World Medical Assembly (Helsinki, 1964) and all applicable amendments established by the World Medical Assemblies, and the ICH guidelines for Good Clinical Practice.
This clinical study will be conducted in compliance with all international laws and regulations; national laws and regulations of the country in which the clinical study is performed; as well as any other applicable guidelines.

15.1. Responsibilities of the Investigator(s)

The Investigator(s) undertake(s) the responsibility to perform the study in accordance with this Protocol, Good Clinical Practice, and the applicable regulatory requirements. The Investigator is required to ensure compliance with the investigational product schedule, visits schedule, and procedures required by the protocol. The Investigator agrees to provide all information requested in the Case Report Form (CRF) in an accurate and legible manner. The investigator may implement a deviation from, or a change of, the protocol to eliminate an immediate hazard(s) to study subjects without prior EC approval/favorable opinion. As soon as possible, the implemented deviation or change, the reasons for it, and, if appropriate, the proposed protocol amendment(s) should be submitted. The investigator must have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the study to conduct the study properly and safely.

15.2. Ethics Committee (EC) Approvals

This clinical study protocol as well as the Informed Consent are to be submitted to the appropriate Ethics Committee, and it is mandatory to obtain the written and dated approval, signed by the chairman with Ethics Committee(s) composition.
The clinical study the documents reviewed, the list of voting members and their qualifications, and the date of the review should be clearly stated on the written Ethics Committee approval.

15.3. Other Ethical Considerations

NA

16. GENDER MEDICINE IN RESEARCH PROTOCOL

The concept of Gender Medicine relies on the idea that health differences between men and women are not only due to their biological attributes and reproductive functions (as defined by biological sex), but also to environmental, social, cultural, and relational factors (as defined by the term gender). According to the Italian Plan for Gender Medicine, accounting for sex and gender in health research is a necessary tool to achieve excellent, rigorous, and reproducible results for the benefit of everybody. When evaluating and treating diseases, **in addition to biological sex other parameters such as age, gender, ethnicity, cultural background, religion, sexual orientation, socio-economic status,** need to be considered to optimize prevention, diagnosis, therapy and care appropriately. Under this perspective special attention needs to be paid to critical health issues relative to transgender and intersexual people.
During the development of research questions, investigators should use the correct terminology, and report (where relevant) whether sex and/or gender may be important variables and differences may be expected at the light of current literature. Thus, investigators should report how sex and/or gender were taken into account in study design and statistics or clarify the reasons for not using a gender medicine approach.
Methodological choices about sex and gender in relation to study population and analytical approach should be reported and justified in the same way as other methodological choices.

The population of the study should be appropriate to capture gender and/or sex-based factors.
The inclusion and exclusion criteria should be well justified with respect to sex and/or gender.
Considerations about anatomical and physiological differences between men and women (height, weight, body mass, cell counts, hormonal cycles, etc.) and social and cultural variables (socio-economic status, education, etc.) should be applied whenever relevant to the topic of the study.
Data on enrolment, participation, dropout, discontinuation and loss-to-follow up should be reported disaggregated by sex and gender (whenever possible).

For guidance, see NIH Policy on Sex as a Biological Variable and SAGER (SexAndGenderEquity in Research) Guidelines.

17. QUALITY ASSURANCE AND QUALITY CONTROL

The study will be conducted in accordance with the current approved protocol, GCP, relevant regulations, and standard operating procedures. Investigators involved in the study will permit study-related audits, EC review, and regulatory inspections by providing direct access to all study records.

Study audits can be conducted by or on behalf of CTC, according to OSR quality standards. Data will be evaluated for compliance with the protocol and accuracy in relation to source documents. Following written standard operating procedures, the auditors will verify that the

clinical study is conducted, and data are generated, documented, and reported in compliance with the protocol, GCP, and the applicable regulatory requirements.

The Investigator should notify the CTC promptly of any inspection scheduled by any regulatory authorities and will promptly forward copies of any inspection reports received.

Not performed by a CRO

17.1. Deviation from study protocol

A deviation from the protocol is an unintended departure from the procedures or processes described in the protocol and approved by the EC.
The Investigator or designee must document and explain in the patient's source documentation any deviation from the approved protocol.
Every deviation from the study protocol must be specified and documented separately for each patient. The investigator should discuss the type and extent of deviation as well as the possible consequences for further participation of the patient in the study.

17.2. Surveillance for observational studies with additional procedure

- NA

18. FINANCE AND INSURANCE

18.1. Funding

NA

18.2.Patient Insurance

NA

19. END OF CLINICAL STUDY

In accordance with applicable regulation, ICH GCP and SOPs, the PI shall notify the end of the clinical study within 15 days from the end of the clinical study and the reasons for such action.

19.1. Summary of the results of the clinical study

Irrespective of the outcome of a clinical study, within one year from the end of a clinical study, the PI shall submit a summary of the results of the clinical study.

20. INTELLECTUAL PROPERTY

As Sponsor of the study, the sole owner of the data and results deriving from this study is IRCCS Ospedale San Raffaele.

21. PUBLICATION POLICY

NA

22. REFERENCES

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APPENDIX A: AMENDMENT HISTORY

Amendment No.	Protocol Version No.	Date issued	Rationale	Study status	Details of Changes

23. APPENDIX B: LIST OF CLINICAL SERVICES / LABORATORIES

Name	Institution	Responsible person	Activity/service	Notes

24. APPENDIX C: LIST OF ENROLLING SITES

NA