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The DiNAM-EoE-C Study

(Esophageal Distensibility and Novel Assessment of Motility in a Eosinophilic Esophagitis Cohort with residual symptoms despite histological remission)

Acronym: DiNAM-EoE-C

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1. Timelines

Start of Study and Data Collection	May 2026
End of Patient Enrollment:	May 2027
End of Study:	August 2027
Final Study Report:	December 2027

2. Background and Rationale

Eosinophilic esophagitis (EoE) is a chronic immune-mediated disorder characterized by esophageal symptoms (e.g., dysphagia, chest pain, food impaction) and eosinophil-predominant inflammation, which may progress toward a fibrostenotic phenotype[1,2]. Endoscopic findings frequently include rings and strictures, which may significantly impair quality of life[3]. Although several therapeutic options are available to reduce inflammation and prevent fibrostenotic progression[1,2], a subset of patients remains symptomatic despite achieving histological remission (<15 eosinophils/HPF). In such cases, endoscopic dilation is often performed empirically to improve esophageal compliance[1,2]. The Functional Lumen Imaging Probe (FLIP) is an emerging tool for assessing esophageal biomechanical properties, particularly distensibility, and is currently considered complementary to high-resolution manometry (HRM) in evaluating esophageal disorders[4,5]. Reduced esophageal distensibility has been associated with an increased risk of food impaction and need for dilation[6-10]. Therefore, the ability of EndoFLIP to detect reduced esophageal distensibility in patients with EoE would allow the identification of those in whom endoscopic dilation may be truly beneficial. Additionally, patients with EoE may exhibit adaptive behaviors and hypervigilance, even in histological remission, potentially influencing symptom perception[11,12]. Persistent inflammation may also lead to esophageal dysmotility, detectable by HRM. According to Statement 22 of the Italian EoETALY 2024 guidelines[2], HRM is recommended to exclude motility disorders in symptomatic patients with histological remission, while serial FLIP assessment may guide the indication for endoscopic dilation.

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3. Aims

The overall aim of this study is to evaluate patients with EoE in histological remission who continue to experience persistent symptoms. The primary objective of the study is to assess changes in esophageal distensibility, as measured by FLIP, before and after endoscopic dilation.

The secondary aims of the study are:

1) To assess the presence of esophageal motility abnormalities using HRM prior to endoscopic dilation;
2) To evaluate the role of hypervigilance in symptom perception in this subgroup of patients;
3) To correlate biomechanical and motility changes with clinical outcomes.

4. Methods

a. Study design

Prospective, multicenter, non-pharmacological, non-profit observational cohort study.

i. Primary Endpoint

Change in esophageal distensibility (i.e., distensibility plateau and esophageal body compliance), measured by FLIP, between baseline (pre-dilation) and follow-up (8–12 weeks post-dilation).

ii. Secondary Endpoints

1. Prevalence (expressed as a percentage) of esophageal motility disorders in symptomatic patients in histological remission, assessed by esophageal HRM;
2. Prevalence (expressed as a percentage) of esophageal hypervigilance in patients in histological remission with persistent symptoms, assessed using EHAS scores at baseline and follow-up;
3. Achievement of clinical response at follow-up (defined as EEsAI < 20).

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b. Setting

The DiNAM-EoE-C study is a multicenter investigation conducted across several centers in Italy, with the Gastroenterology and Endoscopy Unit of Policlinico of Milan serving as the coordinating center. Patient recruitment will take place through participating hospital centers, using clinical records, endoscopic reports, manometric evaluations, and validated questionnaires for symptom assessment and quality of life as data sources. The study will begin in May 2026 and end in August 2027, with a one-year enrollment period and a follow-up scheduled 8–12 weeks after endoscopic dilation. During follow-up, patients will be monitored using validated questionnaires and FLIP assessment to evaluate esophageal distensibility. Data collection will be standardized across centers using anonymized databases.

i. Study Population

Twenty-five patients with eosinophilic esophagitis in histological remission and persistent symptoms, enrolled between May 2026 and May 2027.

ii. Inclusion Criteria

Patients meeting all of the following criteria will be included:

- Age ≥ 18 years;
- Confirmed diagnosis of eosinophilic esophagitis in histological remission (<15 eosinophils/HPF);
- Persistent symptoms (e.g., dysphagia, food impaction, chest pain) despite medical or dietary therapy;
- Stable EoE therapy throughout the study duration (proton pump inhibitors, budesonide, dupilumab, dietary therapies);
- Signed informed consent.

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iii. Exclusion Criteria

Patients who do not meet inclusion criteria or who meet at least one of the following criteria will be excluded:

- Previous diagnosis of severe erosive esophagitis (Los Angeles grade C or higher);
- Previous diagnosis of esophagogastric junction outflow disorders (e.g., achalasia);
- Systemic diseases involving the esophagus (e.g., scleroderma);
- Use or initiation during the study of immunosuppressive or biological drugs, or medications affecting esophageal motility (opioids, nitrates, calcium channel blockers);
- Presence of R3 and/or S1 (according to EREFS).

iv. Description of the Study Object (DiNAM-EoE-C)

The DiNAM-EoE-C study aims to investigate changes in esophageal distensibility using the Functional Lumen Imaging Probe (FLIP) before and after endoscopic dilation in patients with eosinophilic esophagitis in histological remission who continue to experience persistent symptoms. The study will be conducted according to routine clinical practice.

Patients will be adequately informed about the study objectives, procedures, and potential benefits and risks. Each participant will receive a detailed informed consent form outlining the study rationale, the type of assessments to be performed (FLIP, HRM, and validated questionnaires assessing symptoms and quality of life), the duration of follow-up, and any potential discomfort associated with participation.

Adherence to ethical standards and Good Clinical Practice will be maintained, guaranteeing voluntary participation and the right to withdraw from the study at any time without any impact on clinical care.

v. Scheduled Visits and Assessments

The DiNAM-EoE-C study includes a structured schedule of patient visits and assessments, organized into two main phases: baseline and follow-up. During the baseline phase (T0), patients will undergo a comprehensive clinical evaluation, including the administration of validated questionnaires assessing quality of life and symptom perception (EEsAI, I-SEE, EoE-QoL-A, EHAS), as well as instrumental diagnostic testing such as HRM to identify potential motility disorders. During the endoscopic session,

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esophageal distensibility will be assessed using FLIP, after which patients will undergo endoscopic dilation performed with Savary rigid dilators of progressively increasing diameter, in accordance with international guidelines. During the second phase (follow-up), scheduled 8–12 weeks after endoscopic dilation, a comprehensive reassessment will be performed, including the administration of the same symptom and quality-of-life questionnaires and repetition of the FLIP examination to evaluate any improvement in esophageal distensibility.

c. Variables

The variables to be collected in the study include:

- **Demographic and medical history data:** date of birth, age, sex, BMI, smoking status, presence of rhinitis, asthma, atopic dermatitis, food allergy, and eosinophilic gastroenteritis (EoGE);
- **Clinical data at diagnosis:** date of symptom onset, date of diagnosis, diagnostic delay (in months), symptoms at diagnosis (food impaction, chest pain, epigastric discomfort, dysphagia, heartburn, regurgitation, vomiting, odynophagia);
- **Endoscopic and histological data at diagnosis:** EREFS score (edema, rings, exudates, furrows, strictures), eosinophil count per HPF in the proximal and distal esophagus;
- **Previous treatments:** prior use of proton pump inhibitors (PPIs), fluticasone, budesonide, monoclonal antibodies, elimination diet, esophageal dilations (including months since last dilation);
- **Clinical data at baseline (T0):** presence of symptoms, EEsAI, I-SEE, EoE-QoL-A, EHAS, and PiEAQ scores;
- **Manometric data at baseline (T0):** diagnosis according to the Chicago Classification v4.0;
- **Endoscopic data at baseline (T0):** EREFS score (edema, rings, exudates, furrows, strictures);
- **FLIP data at baseline (T0):** proximal and distal esophageal diameter, esophagogastric junction diameter, esophageal contractile response, distensibility index, distensibility plateau (DP), and compliance;
- **Dilation-related data:** date of the procedure, Savary dilation diameters, presence of lacerations, complications;

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- **Clinical data at follow-up (8–12 weeks, T12):** presence of symptoms, EEsAI, I-SEE, EoE-QoL-A, EHAS, and PiEAQ scores;
- **Endoscopic data at follow-up (8–12 weeks, T12):** EREFS score (edema, rings, exudates, furrows, strictures);
- **FLIP data at follow-up (8–12 weeks, T12):** proximal and distal esophageal diameter, esophagogastric junction diameter, esophageal contractile response, distensibility index, distensibility plateau, and compliance.

d. Source Documents

The study is based on clinical data from patients already followed in our Center, as well as on data collected through validated questionnaires (EEsAI, I-SEE, EoE-QoL-A, EHAS, and PiEAQ) and instrumental investigations (HRM, EGD, FLIP) performed before and after endoscopic dilation. Data derived from HRM and FLIP will be stored in digital format and analyzed using dedicated software for processing tracings and calculating esophageal distensibility and pressure values. Data collected through EGD will include endoscopic images. These images will allow the assessment of fibrostenotic features (rings, strictures) or other structural abnormalities. All documents generated during the study will be stored in dedicated digital platforms (Ambweb, Order Entry, RIS) currently in use at the Center and will be digitally signed, according to standard practice, by specialists in Gastroenterology to ensure their clinical validity and medico-legal accountability.

e. Sample Size

In the study by Carlson et al.[8], EoE patients with values within the normal range showed a median distensibility plateau (DP) of 19 mm (IQR 19–20) and a median esophageal body compliance of 691 mm^3/mmHg (IQR 613–828). In contrast, EoE patients classified as fibrostenotic with normal esophageal body reactivity—and therefore with symptoms presumably attributable exclusively to an obstructive mechanism due to esophageal wall stiffness—showed a median DP of 15 mm (IQR 14–17) and a median esophageal body compliance of 393 mm^3/mmHg (IQR 335–497). The distensibility plateau was selected as the primary parameter for sample size calculation, as it represents a direct measure of esophageal wall

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distensibility and serves as the basis for calculating esophageal body compliance. Sample size estimation was performed using a paired Student's t-test, with an alpha level of 0.05 and a power of 90%, assuming a clinically meaningful difference of 2 mm in DP and an estimated standard deviation of 2.2 mm, based on data reported by Carlson et al[8]. According to these assumptions, the minimum required sample size was 14 patients. Considering a 15–20% margin for dropouts and incomplete data, an appropriate sample size would be 16–17 patients. Since the study also aims to explore the role of hypervigilance and potential motility disorders in the persistence of symptoms, it cannot be assumed that all included patients will present significant esophageal stiffness attributable to a fibrostenotic phenotype. This expected heterogeneity in the underlying pathophysiology necessitates an increased sample size to ensure adequate representativeness and the ability to detect clinically meaningful differences between subgroups.

Therefore, the sample size was increased by approximately 30%, reaching a total of 25 patients, in order to support: (1) exploratory analyses of correlations between biomechanical/motility parameters, symptoms, and hypervigilance; (2) identification of pathophysiological subgroups based on FLIP and HRM measurements; and (3) improved reliability of questionnaire-based estimates.

f. Data Management

At the time of enrollment, each participant will be assigned a unique identification code. Data will be de-identified in such a way that individuals accessing the database will not be able to trace back to the identity of the subjects. Only local investigators will be able to link the identification code to the enrolled participants. All study data will be recorded in a dedicated electronic case report form (eCRF) within a Data Management System validated according to national regulations and provided by the Scientific Directorate of the Foundation. The platform used will be REDCap (Research Electronic Data Capture). The REDCap Consortium includes more than 1,000 institutional partners worldwide (research institutions, universities, ministries, etc.). It supports a secure web-based application designed exclusively for data capture in research studies. REDCap allows users to rapidly and securely create and manage online databases and is currently used for over 110,000 projects by approximately 150,000 users across a wide range of research areas. Through REDCap, the following measures will be implemented for this study:

a) user-level access control with role-based restrictions;

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b) real-time data validation and integrity checks;

c) de-identification of patient data prior to export;

d) centralized data storage with daily backup on a secure server within the Foundation's IT infrastructure.

g. Data Analysis

The statistical analysis will primarily include descriptive and inferential methods, using parametric or non-parametric tests depending on the distribution of the variables. Specifically:

1. Descriptive Analysis
   - Continuous variables will be reported as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on their distribution (normal or non-normal).
   - Categorical variables will be presented as absolute frequencies and percentages.
2. Pre–Post Comparison Analysis
   - To compare esophageal parameters before and after dilation, paired Student's t-tests will be used for normally distributed data, while the Wilcoxon signed-rank test will be applied for non-normally distributed data.
   - For categorical variables, Fisher's exact test or the chi-square test will be used, depending on the sample size within each category.
3. Correlation Analysis
   - Relationships between changes in esophageal distensibility, symptom improvement, and hypervigilance will be assessed using Pearson correlation (for normally distributed data) or Spearman correlation (for non-normally distributed data).
4. Multivariate Regression Analysis for Confounding Factors
   - To control for potential confounders (e.g., age, disease duration, baseline histological severity), multivariable linear regression models will be used for continuous outcomes (e.g., change in esophageal distensibility after dilation), and logistic regression models will be applied for categorical outcomes (e.g., clinical improvement yes/no).

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h. Quality Control

To ensure adequate quality control of the study, the investigator will allow, upon request, direct access to all relevant documentation and will dedicate part of their time to discuss the study results. In addition, Regulatory Authorities may conduct inspections. In such cases, the investigator must grant the inspector direct access to all relevant documentation and allocate sufficient time, as well as staff resources, to discuss monitoring findings and any other aspects of the study. For all manual data entries, a double-check procedure involving two operators will be implemented to minimize the risk of errors.

i. Study Limitations

The main limitations of the study include the relatively small sample size of only 25 patients, which may limit the generalizability of the results and reduce the statistical power to detect smaller effects. Furthermore, the non-randomized and uncontrolled design of the study may introduce bias in evaluating the effects of endoscopic dilation, particularly due to the absence of a control group. Another limitation is the potential inter-center variability in the implementation of procedures and data collection, despite the use of standardized protocols.

5. Protection of Enrolled Subjects

The study will be conducted in accordance with Good Clinical Practice (GCP), the ethical principles outlined in the Declaration of Helsinki, and applicable regulations governing observational studies. The observational study and its related documentation will be submitted to the appropriate Ethics Committee. The study will commence only after obtaining all required approvals in accordance with the institution's internal procedures. The Ethics Committee will also review and approve any amendments to the protocol, as well as any materials used for subject recruitment, in compliance with local regulations.

- Patient Information Notice and Informed Consent for Personal Data Processing

It is the responsibility of the investigators to obtain informed consent for the patient information notice, including privacy consent, signed and dated by each participant prior to the start of data collection. The

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signature confirms that the patient has understood the information provided and the contents of the consent forms. In addition, the investigator must sign and date the informed consent form. Signed documents must be retained by the investigator, while a copy must be provided to the patient. The Principal Investigator guarantees that all data collected from enrolled patients will be handled, stored, and processed in full compliance with applicable data protection regulations, including Article 13 of Regulation (EU) 2016/679 (GDPR), current national data protection laws, the Code of Conduct for the processing of personal data for statistical and scientific purposes, and the "Guidelines for the processing of personal data in clinical trials of medicinal products" published in the Italian Official Gazette No. 190 of August 14, 2008. Patient data will be collected in a pseudo-anonymized form and will be accessible only to authorized internal and external personnel who are bound by confidentiality obligations regarding any information acquired during the study. The Principal Investigator further ensures that appropriate technical and organizational measures, as required by the aforementioned regulations, have been implemented for both electronic and non-electronic data processing, in order to prevent unauthorized or unlawful data processing.

- Insurance Coverage

Given the observational nature of the proposed study, no additional insurance coverage is required beyond that already provided for routine clinical practice.

6. Dissemination and Communication Plan of Study Results

The scientific lead of the study will be responsible for preparing a final report and for disseminating the study results upon completion. The data will be made publicly available in anonymized form and presented, where required, in aggregated format.

7. Funding

No external funding.

8. References

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9. Abbreviation

- DP: Distensibility Plateau
- eCRF: Electronic Case Report Form
- EGD: Esophagogastroduodenoscopy
- EHAS: Esophageal Hypervigilance and Anxiety Scale
- EEsAI: Eosinophilic Esophagitis Activity Index
- EoE: Eosinophilic Esophagitis
- EoE-QoL-A: Eosinophilic Esophagitis Quality of Life – Adult
- EREFS: Endoscopic Reference Score
- FLIP: Functional Lumen Imaging Probe
- HRM: High-Resolution Manometry
- I-SEE: Index of Severity for Eosinophilic Esophagitis
- PiEAQ: Pisa EoE Adaptation Questionnaire
- PPI: Proton Pump Inhibitors
- T0: Baseline (Initial Timepoint)
- T12: Follow-up at 8–12 Weeks