CLINICAL STUDY PROTOCOL

Grupo de Estudo da Doença Inflamatória Intestinal (GEDII)

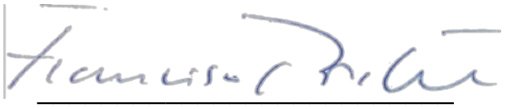
Title: Iron deficiency in inflammatory bowel disease. Correlation with inflammation and Vitamin D status

Study code: **ID_IBD**

Type of study: Observational

Date of protocol: *06 Jun 2019*

Version no.: 1

Study Sponsor:	Grupo de Estudo da Doença Inflamatória Intestinal (GEDII)
Name of Scientific Coordinator	Francisco Portela
Signature and Date	 25/11/2019
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PRINCIPAL INVESTIGATOR SIGNATURE PAGE *(to be signed by the PI from each participating center)*

Study Title: Iron deficiency anemia in inflammatory bowel disease. Correlation with inflammation and Vitamin D status

Study Code: ID_IBD

Protocol Version/Date: version 1/06 June 2019

Center Name: _____

Principal Investigator:

Name:

Academic degree:

Address:

Phone:

Email:

I, the undersigned, am responsible for the conduct of the study at this site and affirm that:

I understand and will conduct the study according to the protocol, any approved protocol amendments, and all applicable Health Authority requirements and national laws.

I will not deviate from the protocol without prior written permission from the GEDII, except where necessary to prevent immediate danger to the subject.

Signature Date of Signature

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1. Synopsis

Title:	Iron deficiency in inflammatory bowel disease. Correlation with inflammation and Vitamin D status
Study Code:	**ID_IBD**
Scientific Coordinator:	Francisco Portela
Disease/Condition	Crohn's disease and Ulcerative colitis
Rational	There is limited data on role of vitamin D as a regulator of iron status and development of iron deficiency anemia in the context of adult IBD populations. Taking advantage of a valuable tool such as the GEDII Registry, this study aims to assess the impact of vitamin D and inflammation levels on iron status as well as other clinical and biomarker outcomes among patients with CD and UC. The study will follow a cohort of IBD patients registered in the GEDII Registry. The primary objective of this study is to explore the prevalence of iron deficiency in patients with IBD and clarify the impact of vitamin D as well as the level of the inflammation (evaluated through inflammatory markers and activity indexes). In parallel, the study also aims to analyze the etiology of anemia in patients with IBD and evaluate the impact of anemia and iron deficiency on quality of life and fatigue.
Research hypothesis:	We hypothesize that iron deficiency, in patients with IBD, is correlated with vitamin D levels, as well as levels of inflammation.
Primary Objectives:	Among patients with CD and UC at study inclusion, registered in the GEDII Registry: • To measure the prevalence of iron deficiency and characterize the patient population with this condition. • To evaluate the impact of vitamin D levels on iron status. • To evaluate the impact of inflammation levels on iron status. • To assess the correlation between hepcidin levels and levels of vitamin D, as well as iron status.
Secondary Objective(s):	• To explore the etiology of anemia in patients with IBD. • To evaluate the impact of anemia and iron deficiency on quality of life. • To evaluate the impact of anemia and iron deficiency on fatigue.
Study Design:	This is a multicenter, cross-sectional, competitive, observational study designed to gather and analyze data on a consecutive cohort of subjects with CD and UC. There is no imposed experimental intervention and prescribing decisions from the study physicians will be independent of patient's participation in this study. The study will analyze a consecutive sample of 300 patients who are registered in the GEDII Registry and who fulfill the protocol's eligibility criteria. The recruitment period is 6 months but may be extended if the target number of participants is not achieved within the defined timeframe. The study will start on the day of the study visit of the first included patient and will run, within the defined period, until the defined number of patients is attained. Socio-demographic and clinical data will be collected in the study visit, as well as patient reported outcomes (IBDQ Index and Fatigue Index). A total of 6 centers are expected to participate.
Inclusion Criteria:	Patients will be included if all the following criteria are met: 1. Patients ≥18 years-old at the date of inclusion; 2. Patients who are registered in the GEDII Registry; 3. Patients diagnosed with IBD at least 3 months before inclusion; 4. Patients who provided their informed consent.
Exclusion Criteria:	Patients will be excluded if <u>at least one</u> of the following criteria is met: 1. Patients who were treated with antibiotics in the last month; 2. Patients who underwent surgery in the last 3 months; 3. Patients with diagnosis of hematologic disease; 4. Patients who are not willing to comply with routine clinical appointments.

Expected number of patients:	300 patients
Expected number of sites:	Approximately 6 centers are expected to participate.
Subject selection:	The study will analyze a consecutive sample of 300 patients who are registered in the GEDII Registry and who fulfill the protocol's eligibility criteria. The recruitment period is 6 months but may be extended until the target number of participants is achieved.
Exposure of interest:	Iron deficiency is the exposure of interest. The correlation with inflammation levels and vitamin D will be evaluated.
Main data collected:	Socio-demographic and clinical data will be collected in the study visit, as well as patient reported outcomes (IBDQ Index and Fatigue Index).
Endpoints	**Primary endpoints:** • Proportion of patients with iron deficiency. • Correlation between vitamin D levels and iron deficiency. • Correlation between vitamin D levels and hepcidin levels. • Correlation between inflammation levels and iron deficiency. • Correlation between hepcidin levels and iron deficiency. **Secondary endpoints:** • Proportion of patients with different etiologies of anemia. • Patient-reported fatigue status assessed by the Fatigue Index – FACIT. • Patient-reported quality of life assessed by the IBDQ Index.
Statistical methods	Categorical variables will be described through absolute and relative frequencies. Continuous variables will be described through mean and standard deviation or median and percentiles, according to the symmetry of the distribution. Scales and subscales of the analyzed instruments will be calculated considering the indications of the authors of the original versions. Additionally, we will test hypothesis on the distribution of continuous variables with non-normal distribution through the non-parametric test of Mann-Whitney or Kruskal-Wallis, depending on the nature of the tested hypothesis. The association of two categorical variables will be tested through the Chi-Square test or Fisher Exact test, as appropriate. The evaluation of the association of the variables under analysis will be performed resorting to the calculation of correlation coefficients (Pearson/Spearman*)*, with construction of the corresponding dispersion matrix. Regarding the factors associated to anemia, we will resort to multivariate logistic models and estimate the corresponding measures of association – Odds Ratios (OR) and the respective 95% confidence intervals.
Overall Study Duration:	The study will last until the defined number of patients is recruited and included.
Study timelines:	The study is expected to start during the 2nd semester of 2019. Study closure is expected to occur in 1st semester of 2020.

2 INTRODUCTION

2.1 INFLAMMATORY BOWEL DISEASE (IBD)

Inflammatory bowel disease (IBD) is a chronic and disabling condition with an increasing incidence in southern Europe. The etiology of IBD remains unknown, but the characteristic disproportionate inflammatory response in the gut may develop through various mechanisms at the cellular and subcellular level.[1] Ulcerative colitis (UC) and Crohn's disease (CD) represent the two main types of IBD.

Ulcerative colitis is a relapsing non-transmural inflammatory disease that is restricted to the colon. Patients typically present bloody diarrhea (often nocturnal and postprandial), passage of pus, mucus or both, and abdominal cramping during bowel movements. Crohn´s disease is a relapsing, transmural inflammatory disease of the gastrointestinal mucosa that can affect the entire gastrointestinal tract from the mouth to the anus. Typical presentations include the discontinuous involvement of various portions of the gastrointestinal tract and the development of complications including strictures, abscesses, or fistulas.[2]

In Portugal, the prevalence of IBDs increased from 86 to 146 people per 100 000 inhabitants between 2003 and 2007. Within the same timeframe, the prevalence of UC and CD increased from 42 to 71 people per 100 000 inhabitants and from 43 to 73 persons per 100 000 inhabitants, respectively. IBDs are more prevalent among women.[3]

2.2 IRON DEFICIENCY AND VITAMIN D

Iron deficiency is a frequent complication of IBD and one of the main causes of anemia in these patients.[4,5] The reported prevalence of anemia in IBD varies widely between different populations, depending on the specific characteristics of each studied group.[5] The impact of iron deficiency on quality of life is well documented; studies from different geographical regions,[6,7] including Portugal,[5] analyzed the prevalence of this complication. Based on these results, objective orientations for the treatment of this condition were developed.[4]

Iron deficiency without anemia is less well studied, either in terms of prevalence, etiologic factors and need for treatment. In IBD, iron deficiency can be associated with insufficient dietary iron ingestion, hematic losses (resulting from intestinal lesions) or reduced iron absorption, which is mediated by increased hepcidin levels due to the inflammatory state.[8,9] In the presence of inflammation, hepcidin levels increase, via cytokine stimulation, and iron absorption is reduced due to the binding of hepcidin to ferroportin, the transmembrane iron transporter. However, the assessment of iron status in the context of inflammatory disease is challenging, because the mediators of inflammation can have a meaningful impact on the markers of iron status. This leads to difficulties in diagnosing states of iron deficiency as well as defining adequate treatment strategies.

2.3 ROLE OF VITAMIN D IN THE REGULATION OF IRON LEVELS

Vitamin D is a nutrient with systemic effect, which is regulates both the innate and adaptive immune response.[10] Its immuno-inflammatory properties, such as the reduction of pro-inflammatory cytokines, are associated with a direct effect on hepcidin through the HAMP (hepcidin antimicrobial peptide) pathway and, thus, this poses vitamin D as a potential regulator of iron availability for erythropoiesis.

This possibility was already demonstrated in other diseases such as heart failure[11] and even the pediatric IBD population,[11–13] but it not well studied in adult IBD patients.

The recent change of paradigm in the therapeutic goals of IBD, namely through the "treat to target" strategy[14] means that for the iron status makers to be considered, the clinical impact should be demonstrated and supported by robust data.

2.4 THE GEDII REGISTRY

Patient registries are a powerful tool to observe the course of disease, understand variations in treatment and outcomes, to assess effectiveness, to monitor safety and harm and to examine factors that influence prognosis and quality of life. They are also useful to describe patterns of care and to actually measure the quality of care.

From a clinician's perspective, registries can collect data about disease presentation and outcomes on large numbers of patients rapidly, thereby producing a real-world picture of disease, current treatment practices, and outcomes. A registry might also provide data that can be used to assess the degree to which clinicians are managing a disease in accordance with evidence-based guidelines, focus attention on specific aspects of a particular disease that might otherwise be overlooked, or provide data for clinicians to compare themselves with their peers. Overall, the use of patient registries appears to be active and growing.[15]

The "Grupo de Estudo da Doença Inflamatória Intestinal" (GEDII) Registry was created on 2005 and allows the regular and systematic capture of socio-demographic and clinical characteristics of patients diagnosed with IBDs (CD, UC and indeterminate UC). The Registry also captures the clinical and safety outcomes, treatments and the use of health resources.

So far, the Registry covers 20 gastroenterology departments of public hospitals. As of December 2018, the Registry comprised a total of 3800 adult patients and 400 pediatric patients.

2.5 RATIONALE

There is limited data on role of vitamin D as a regulator of iron status and development of iron deficiency anemia in the context of adult IBD populations. Taking advantage of a valuable tool such as the GEDII Registry, this study aims to assess the impact of vitamin D and inflammation levels on iron status as well as other clinical and biomarker outcomes among patients with CD and UC. The study will follow a cohort of IBD patients registered in the GEDII Registry and who were diagnosed at least 3 months prior to inclusion.

The primary objective of this study is to explore the prevalence of iron deficiency in patients with IBD and clarify the impact of vitamin D as well as the level of the inflammation (evaluated through inflammatory markers and activity indexes).

In parallel, the study also aims to analyze the etiology of anemia in patients with IBD and evaluate the impact of anemia and iron deficiency on quality of life and fatigue.

2.6 RESEARCH HYPOTHESIS

We hypothesize that iron deficiency, in patients with IBD, is correlated with vitamin D levels, as well as levels of inflammation.

3 OBJECTIVES

3.1 PRIMARY OBJECTIVES

Among patients with CD and UC diagnosed at least 3 months prior to study inclusion, registered in the GEDII Registry:

- To measure the prevalence of iron deficiency and characterize the patient population with this condition.
- To evaluate the impact of vitamin D levels on iron status.
- To evaluate the impact of inflammation levels on iron status.
- To assess the correlation between hepcidin levels and levels of vitamin D, as well as iron status.

3.2 SECONDARY OBJECTIVES

- To explore the etiology of anemia in patients with IBD.
- To evaluate the impact of anemia and iron deficiency on quality of life.
- To evaluate the impact of anemia and iron deficiency on fatigue.

4 STUDY DESIGN

This is a multicenter, cross-sectional, competitive, observational study designed to gather and analyze data on a consecutive cohort of subjects with CD and UC. There is no imposed experimental intervention and prescribing decisions from the study physicians will be independent of patient's participation in this study.
The study will analyze a consecutive sample of 300 patients who are registered in the GEDII Registry and who fulfill the protocol's eligibility criteria. The recruitment period is 6 months but may be extended if the target number of participants is not achieved within the defined timeframe.
The study will start on day of the study visit of the first included patient and will run, within the defined period, until the defined number of patients is attained.
Socio-demographic and clinical data will be collected in the study visit, as well as patient reported outcomes (IBD-Control Questionnaire, IBDQ Index and Fatigue Index).
A total of 6 centers are expected to participate.

5 STUDY TIMELINES

The study is expected to start during the 2nd semester of 2019. The study will last until the planned sample size is achieved.

6 STUDY POPULATION

6.1 INCLUSION CRITERIA

Patients will be included if all the following criteria are met:

1. Patients ≥18 years-old at the date of inclusion;
2. Patients who are registered in the GEDII Registry;
3. Patients diagnosed with IBD at least 3 months before inclusion;
4. Patients who provided their informed consent.

6.2 EXCLUSION CRITERIA

Patients will be excluded if at least one of the following criteria is met:

1. Patients who were treated with antibiotics in the last month;
2. Patients who underwent surgery in the last 3 months;
3. Patients with diagnosis of hematologic disease;
4. Patients who are not willing to comply with routine clinical appointments.

6.3 DISCONTINUATION FROM OBSERVATION PERIOD

In this study, patients will be observed in a single visit. However, data may be excluded if there are evidences of:

- Protocol violation
- Patient withdrawal of consent
- Pregnancy
- Death

In the case of data exclusion, the date of study discontinuation, and the reason for discontinuation should be recorded in the electronic CRF.

7 INFORMATION TO BE COLLECTED

7.1 VARIABLES CAPTURED BY THE GEDII REGISTRY

The GEDII Registry allows the collection of socio-demographic, clinical characteristics and outcomes of patients diagnosed with IBD.

The following variables will be obtained from the Registry:

- Date of birth
- Sex
- Height
- Weight
- BMI
- Diagnosis of IBD and date
- Previous surgery

- History of anemia
- Previous iron supplementation
- Harvey Bradshaw score (5 items: general well-being, abdominal pain, number of liquid or soft stools per day, abdominal mass and complications)
- Partial Mayo scoring system
- Laboratory parameters: hemoglobin, reticulocytes, ferritin, iron, transferrin, sTfR – soluble transferrin receptor, hepcidin, folic acid, vitamin B12 and vitamin D [25(OH)D], calprotectin,
- Previous therapies for IBD (salicylates, corticoids, immunosuppressants, iTNF, vedolizumab, ustecinumab, tofacitinib)
- Current supplementation (iron, vitamin D, vitamin B12, folic acid) or in the previous 6 months

7.2 PATIENT REPORTED OUTCOMES

Patients will be instructed to report on their health at the data collection time point, by filling 3 questionnaires:

- IBDQ Index
- Fatigue Index – FACIT
- Disease activity questionnaire

All information will be collected anonymously.

8 EXPOSURE OF INTEREST

Iron deficiency is the exposure of interest. The correlation with inflammation levels and vitamin D will be evaluated.

9 ENDPOINTS

9.1 PRIMARY ENDPOINT

- Proportion of patients with iron deficiency.
- Correlation between vitamin D levels and iron deficiency.
- Correlation between vitamin D levels and hepcidin levels.
- Correlation between inflammation levels and iron deficiency.
- Correlation between hepcidin levels and iron deficiency.

9.2 SECONDARY ENDPOINTS

- Proportion of patients with different etiologies of anemia.
  Patient-reported fatigue status assessed by the Fatigue Index – FACIT.
- Patient-reported quality of life assessed by the IBDQ Index.

9.3 DEFINITIONS OF INTEREST

Clinical activity

- Crohn's Disease activity assessed by the Harvey Bradshaw Index
- Ulcerative Colitis activity assessed by the Mayo Partial Scoring System

Harvey Bradshaw Index (assessment of Crohn's Disease activity)

1. General well-being (yesterday)
0 = Very well
1 = Slightly below par
2 = Poor
3 = Very poor
4 = Terrible

2. Abdominal pain (yesterday)
0 = None
1 = Mild
2 = Moderate
3 = Severe

3. Number of liquid or soft stools per day (yesterday) = _____
4. Abdominal mass
0 = None
1 = Dubious
2 = Definite
3 = Definite and tender

5. Complications (check any that apply; score one per item except for first box)
- None
- Arthralgia
- Uveitis
- Erythema nodosum
- Aphthous ulcers
- Pyoderma gangrenosum
- Anal fissure
- New fistula
- Abscess

Partial Mayo scoring system (assessment of Ulcerative Colitis clinical activity)

Stool frequency[a]
0 = Normal number of stools for this patient
1 = 1-2 stools more than normal
2 = 3-4 stools more than normal
3 = 5 or more stools more than normal

Rectal bleeding[b]
0 = No blood seen
1 = Streaks of blood with stool less than half the time
2 = Obvious blood with stool most of the time
3 = Blood alone passed

Physician´s global assessment[c]
0 = Normal
1 = Mild disease
2 = Moderate disease
3 = Severe disease

[a] Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency
[b] The daily bleeding score represents the most severe bleeding of the day

[c] The physician´s global assessment acknowledges the 3 other criteria, the patient´s recall of abdominal discomfort and general sense of well-being, and other observations, such as physical findings and the patient´s performance status.

10 STATISTICAL ANALYSIS

10.1 GENERAL CONSIDERATIONS

Categorical variables will be described through absolute and relative frequencies. Continuous variables will be described through mean and standard deviation or median and percentiles, according to the symmetry of the distribution.
Scales and subscales of the analyzed instruments will be calculated considering the indications of the authors of the original versions.
Additionally, we will test hypothesis on the distribution of continuous variables with non-normal distribution through the non-parametric test of Mann-Whitney or Kruskal-Wallis, depending on the nature of the tested hypothesis. The association of two categorical variables will be tested through the Chi-Square test or Fisher Exact test, as appropriate.
The evaluation of the association of the variables under analysis will be performed resorting to the calculation of correlation coefficients (Pearson/Spearman*)*, with construction of the corresponding dispersion matrix.
Regarding the factors associated to anemia, we will resort to multivariate logistic models and estimate the corresponding measures of association – Odds Ratios (OR) and the respective 95% confidence intervals.
In all hypothesis testing a significance level of 5% will be considered.
The analysis will be performed using IBM SPSS Statistics, Version 25. (IBM Corp, Armonk, NY, USA).

10.2 SAMPLE SIZE

This study is expected to include a total of 300 patients. This sample size will allow the evaluation of the potential of vitamin D levels in predicting iron deficiency anemia in patients with IBD. In addition, this sample size will allow the exploratory analysis of association between hepcidin and vitamin D.
Regarding the correlation analysis, with this sample size there is a probability greater than 95% that the lower limit of a one-sided 95% confidence interval is higher than 0.50, if the observed correlation coefficient is at least 0.75.

11 PHARMACOVIGILANCE

New safety findings that can potentially affect the risk/benefit profile of a medicinal product identified during the conduct of epidemiological studies will be reported promptly to the Health Authorities, according to local pharmacovigilance regulations.

12 ETHICAL AND LEGAL ASPECTS

12.1 ETHICS

The study will be conducted according to the ethics principles originated from the Declaration of Helsinki and the Portuguese Clinical Research law (Law #21/2014, 16th April 2014).

A copy of the protocol, proposed informed consent form and other written subject information will be submitted to the competent Ethics Committee for written approval. A copy of the written approval of the protocol and of the informed consent form must be received, by the Investigator, before the recruitment of subjects and data collection are initiated.
The investigator will submit and, where necessary, obtain approval from the competent Ethics Committee for all subsequent protocol amendments and changes to the informed consent document.

12.2 INFORMED CONSENT

Before any protocol specific procedures are performed, the investigator is responsible for obtaining written informed consent from the subject (or authorized representative) and after an adequate and clear explanation of the aims, methods, anticipated benefits, and potential hazards of the study.
The informed consent process should be documented in the subject's medical charts, and the informed consent form should be signed and personally dated by the subject (or authorized representative, if applicable) and by the person who conducted the informed consent discussion (not necessarily an investigator). The original signed informed consent form should be retained in accordance with institutional policy, and a copy of the signed consent form should be provided to the subject or authorized representative.

12.3 STUDY DISCONTINUATION CRITERIA

Premature termination of this study may occur because of a regulatory authority decision, change in opinion of the ethics committee, or at the discretion of the GEDII. If GEDII decides to terminate the study prematurely, GEDII or a designee will promptly notify the appropriate Ethics Committee and regulatory authority (if applicable).

13 QUALITY CONTROL

The study will involve a GEDII monitor who will be responsible for ensuring that the study is conducted according to the protocol and to the local regulatory/ethical requirements.
Before the start of activities, a study monitor will conduct Initiation Visits at the sites in order to train the investigational team on the protocol and other protocol-related procedures.
During the study, the monitor will also be responsible for conducting periodic monitoring visits at the sites to ensure that the protocol is being followed and the data recorded is accurate and collected according to the defined procedures.
The sites may be subject to review by the Independent Ethics Committee and/or to quality assurance audits performed by a GEDII designated representative, and/or to inspection by appropriate regulatory authorities. The Investigator(s) and their relevant staff should be available during the monitoring visits and possible audits or inspections. The investigator and institution will allow the appropriate regulatory authorities direct access to source documents to perform this verification.
Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with this protocol and to give access to all relevant data and records to monitors, auditors, Ethics Committees, and regulatory authorities, as required.

All investigators and study staff will receive training on the protocol and other protocol-related procedures prior to start of activities. The training will be provided by GEDII or its representative.

14 DATA HANDLING

14.1 CONFIDENTIALITY

The investigator is responsible for ensuring that the subject's confidentiality is maintained.
Questionnaires, database and other documents generated in this study will be identified by a unique subject identification number. This 2-digit number will be assigned sequentially, by each investigator, based on subject's recruitment schedule (e.g.: first subject will be assigned No. 01, the second subject will be No. 02 and so on). Each center will also be assigned a predefined two-digit number.
The GEDII Registry received the authorization of Comissão Nacional para Protecção de Dados for the purpose of data processing under the scope of "Lei de Protecção de Dados de Carácter Pessoal Dec. 67/98 de 26 de Outubro".

14.2 DATA COLLECTION

All study data will be obtained from the GEDII Registry, laboratory reports and, when relevant, will be complemented by subject's interview or other medical sources (as appropriate).
The investigator will be responsible for ensuring that all findings and data are accurately and reliably recorded in the case report form.

All eligible subjects who are not enrolled in the study will be recorded in a specific form. No personal data will be collected in this form, only the date of assessment of eligibility criteria and reason for non-enrollment. This form will be kept exclusively at each site.

14.3 STUDY ARCHIVE

The investigator will keep an adequate archive of all study documentation with access restricted to study team. The study archive will be kept at each site for at least 15 years from the study close out.

14.4 PUBLICATION POLICY

All documents and results generated from this clinical study are exclusive property of the Coordinating Investigator and GEDII. Any related publications must be previously approved in written by the Coordinating Investigator and GEDII.
The results of the study will be presented by the Coordinating Investigator in national and international meetings and will be published in international papers.
The study results can only be published after the clinical study is terminated; data analysis is completed only upon the agreement of the study's scientific board. The publication should include the results from all the centers that participated in the clinical investigation. The publication of results should be agreed by all participating investigators and in strict adherence to the principles originated from the Helsinki Declaration and according to Portuguese Clinical Research law (Law #21/2014, 16th April 2014)[20].

Authorship criteria

For all publications related to this study, the GEDII will comply with recognized ethical standards concerning publications and authorship established by the International Committee of Medical Journal

Editors (*Recommendations for the Conduct, Reporting, Editing, and Publication of Scholarly Work in Medical Journals - Updated December 2013*).

For all publications, related with this clinical study, the order of the authors is as follows:

- The first author position will correspond to the Coordinating Investigator;
- The subsequent author's positions will correspond to the principal investigator from each center, who will be ranked decreasingly according to the number of patients included in the study, as far as the number of co-authors allowed by the journal is not exceeded;
- All the participating investigators not figuring in the authorship (due to journal's limitations in the number of co-authors) will be cited in the acknowledgment section of the publication.
- The last author position will correspond to a GEDII member.

15 REFERENCES

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16 APPENDIX – CHRONOGRAM

	Data collection time points
Information to be collected	**Study visit (inclusion)**
Demographics	X
Weight	X
Body mass index	X
Diagnosis	X
Medical history Surgical resection Hospitalizations Anemia	X
Treatment Previous IBD treatment Current IBD treatment Iron (oral/intravenous) Supplementation, current and previous 6 months, iron, vitamin D, vitamin B12, folic acid	X
Disease activity Partial Mayo score (UC) Harvey Bradshaw Index (CD)	X
Local laboratory paraments Hemogram Reticulocytes Folic acid Vitamin B12 C-reactive protein	X
Central laboratory paraments Iron Ferritin Transferrin saturation Soluble transferrin receptor Hepcidin Vitamin D [25(OH)D] Fecal calprotectin	X
Patient-reported outcomes FACIT Index IBDQ Index Disease activity questionnaire	X