CLINICAL STUDY PROTOCOL

NCT Number: NCT04876690

Study Title: Quality of Life of Crohn's Disease Patients With Complex Perianal Fistulas: an Observational, Cross-sectional Study

Study Number: IBD-5007

Protocol Version and Date:

Version 1.0: 25-February-2021

Non-Interventional Study Protocol

Title: Quality of life of Crohn's disease patients with complex perianal fistulas: an observational, cross-sectional study (CONFLICT)

Short title: Quality of life in patients with complex perianal fistulas (CONFLICT study)

Study ID: IBD-5007

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Study phase: Medical Affairs, Post-Approval Company Sponsored (Observational)

Date of version 1 of protocol: 25 Feb 2021

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1.2 Approval

REPRESENTATIVES OF TAKEDA

This study will be conducted with the highest respect for the individual participants in accordance with the requirements of this clinical study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- Guidelines for good Pharmacoepidemiology practices (GPP)
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

SIGNATURES

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INVESTIGATOR SIGNATURE PAGE

I confirm that I have read and that I understand this protocol and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events as defined in this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Provence)

Location of Facility (Country)

STUDY SUMMARY

Name of Sponsor(s): Takeda Farmacêuticos Portugal	**Compound/Product:** Not applicable
Title of Protocol: Quality of life of Crohn's disease patients with complex perianal fistulas: an observational, cross-sectional study (CONFLICT)	
Study Number: IBD-5007	**Phase** Not applicable

Study Design:

This is a national, observational, cross-sectional study primarily aimed at assessing the general Quality of Life (QoL) among Crohn's disease (CD) patients with complex perianal fistulas (CPFs) in the Portuguese routine clinical practice. In addition to the cross-sectional design, the study will have a retrospective component to collect data on healthcare resource utilization and on the pharmacological and surgical treatments used for the management of CPFs in the three years prior to the inclusion visit.

The study will be conducted in five Portuguese public hospitals experienced in the management of patients with CD. Gastroenterologists working at the participating hospitals will participate in the study as investigators. Eligible patients (i.e., meeting all inclusion criteria and no exclusion criteria) will be consecutively enrolled during routine medical appointments at the participating hospitals.

Primary Objective:

1) To assess the general QoL among CD patients with CPFs attending secondary care services in Portugal.

Secondary Objectives:

1) To assess the IBD-specific QoL among CD patients with CPFs.
2) To assess the sexual function among CD patients with CPFs.
3) To assess fecal incontinence among CD patients with CPFs.
4) To assess the work productivity and activity impairment among CD patients with CPFs.
5) To assess the healthcare resource utilization in CD patients with CPFs within the three years prior to the inclusion visit.
6) To describe the sociodemographic, anthropometric, and clinical characteristics of CD patients with CPFs.
7) To describe the pharmacological and surgical treatments used for the management of CPFs within the three years prior to the inclusion visit.
8) To explore the association between general QoL and the sociodemographic, anthropometric, and clinical characteristics of CD patients with CPFs.

Exploratory Objectives:

1) To explore the association between IBD-specific QoL/sexual function and the sociodemographic, anthropometric, and clinical characteristics of CD patients with CPFs.

Subject Population:

Male and female CD patients aged 18 or older with CPF(s).

Sample Size: 80 eligible patients will be included in this study.	**Study Sites:** Five Portuguese hospitals experienced in the management of CD patients.

Duration of Study:

Overall Study Duration (including ethics committees' submissions): 11 months

Enrolment period: 9 months

Treatment/Follow-up: N/A

Criteria for Inclusion:

1. Male or female patients aged 18 years or older at the inclusion visit.
2. Patients diagnosed with CD.
3. Presence of CPF(s), defined as ≥1 of the following criteria:
   - high intersphincteric, high transsphincteric, extrasphincteric, or suprasphincteric location;
   - ≥2 external openings;
   - associated collections.
4. Patients attending routine gastroenterology appointments at the participating hospitals.
5. Patients capable of understanding and complying with protocol requirements, in the investigators' opinion.
6. Patients or, when applicable, the patients' legally acceptable representative, who signed and dated a written informed consent form and any required privacy authorization prior to the initiation of any study procedures.

Criteria for Exclusion:

1. Patients diagnosed with ulcerative colitis or indeterminate IBD.
2. Patients with non-complex fistulas or with fistulas types other than perianal (e.g., rectovaginal).
3. Patients currently participating in any interventional clinical trial.

Endpoints/Outcomes and Measures

Primary endpoint/outcome

1) Meta-scores of the SF-12 questionnaire (physical component score [PCS-12] and mental component score [MCS-12]).

Secondary endpoints/outcomes

1) Short IBDQ (SIBDQ) questionnaire score.
2) SQOL-M and SQOL-F questionnaire scores for male and female patients, respectively.
3) Wexner score.
4) Work Productivity and Activity Impairment (WPAI) questionnaire score.
5) Outpatient visits (gastroenterology or other medical specialty), emergency room visit, hospitalizations (≥24 hours), and pharmacological and surgical treatments used for the management of CPFs within the three years prior to the inclusion visit.
6) Patients' sociodemographic, anthropometric and clinical characteristics.
7) Pharmacological and surgical treatments used for the management of CPFs within the three years prior to the inclusion visit.
8) Association between general QoL (PCS-12 and MCS-12) and the patients' socio-demographic, anthropometric and clinical characteristics.

Exploratory endpoint

1) Association between IBD-specific QoL (SIBDQ score)/sexual function (SQOL-M and SQOL-F scores) and the patients' socio-demographic, anthropometric and clinical characteristics.

Statistical Considerations:

Primary analysis

The results obtained for each item of the SF-12 will be summarized in a frequency table, including counts (n) and percentages (%). The two resulting meta-scores – the physical health composite scale score and the mental health composite scale score – will be summarized by descriptive statistics, namely mean (with 95% confidence intervals), standard deviation, median, range (minimum and maximum values) and interquartile ranges.

Secondary analyses

IBD-specific QoL, sexual function, fecal incontinence and impact on social/work activities and work productivity

The results obtained for the remaining study questionnaires (SIBDQ, SQOL-M, SQOL-F, WPAI, and Wexner score) will be summarized as described for the primary analysis, with qualitative items/questions being summarized by counts (n) and percentages (%) and quantitative items/questions summarized by descriptive statistics, namely mean, standard deviation, median, range (minimum and maximum values) and interquartile ranges.

Healthcare Resource Utilization

Data on outpatient visits (number, medical specialty), emergency room visits (number), hospitalizations ≥24 hours (number, length of stay, ICU admission, ICU length of stay), and pharmacological and surgical treatments used for CPF management (number) within the three years prior to the inclusion visit will be summarized descriptive statistics – namely mean, standard deviation, median, range (minimum and maximum) and interquartile ranges – or by absolute (n) and relative (%) frequencies, as applicable. Moreover, the number of patients with at least one outpatient visit, emergency room visit, and hospitalization ≥24 hours will be presented.

Patients' characteristics

All patients sociodemographic, anthropometric and clinical characteristics will be summarized by descriptive statistics – namely mean, standard deviation, median, range (minimum and maximum) and interquartile ranges – or by absolute (n) and relative (%) frequencies, as applicable.

Pharmacological treatments and surgeries for CPF

The pharmacological and surgical treatments used for the management of CPF will be described by counts (n) and percentages (%). For each pharmacological treatment (antibiotics, monoclonal antibodies and immunosuppressants), patients will be divided into three categories (current users, past users, and non-users) considering the three years prior to the inclusion visit. Current combinations (i.e., combinations used by the patient at the inclusion visit) will be described by counts (n) and percentages (%).

Factors associated with general QoL (SF-12)

Associations between general QoL (for the two SF-12 meta-scores – PHC and MHC) and qualitative variables will be tested with the t-test for independent samples/ANOVA for two/three or more independent samples or with the Mann-Whitney/Kruskal-Wallis non-parametric tests, according to the assumption validations of the statistical test. Associations between general QoL (for PHC and MHC) and quantitative variables will be performed through Pearson correlation coefficient or Spearman correlation coefficient (in case the normality assumption is not verified).

Moreover, linear multiple regressions will be used to explore the association between the dependent variable (PCS and MCS meta-scores of the SF-12) and independent variables of interest according to the bivariate analysis results. Regression coefficients (B) and 95% confidence intervals will be computed to measure the magnitude of these associations.

Exploratory analyses

The same methodology described above for factors associated with general QoL (SF-12) will be followed to explore the association between independent variables of interest and the following dependent variables:

- IBD-specific QoL (SIBDQ score).
- Sexual function (SQOL-M and SQOL-F scores for male and female patients, respectively).

Sample Size Justification:

The sample size was determined based on the study's primary objective. To determine the sample

size, an expected standard deviation of the outcome (SF-12 score) is required. Ideally, a standard deviation of the SF-12 score assessed in CD patients with CPFs should be used. However, we found no studies in the literature reporting SF-12 scores exclusively for CD patients with CPFs. Alternatively, we used the data reported by a study that evaluated the QoL via SF-12 in CD patients (25). This study reported mean scores of 49.1 (±10.2) and 49.6 (±10.6) for PCS-12 and MCS-12, respectively.

Considering an expected standard deviation of 10.6 (the most conservative) based on the abovementioned study, a confidence level at 95% and a margin of error of approximately 2.3, a total of 80 patients should be included in the study to assess the general QoL via the SF-12 questionnaire.

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List of Abbreviations and Definition of Terms

AE:	Adverse Event
AE:	Adverse Drug Reaction
AGA:	American Gastroenterological Association
CA:	Competent Authority
CD:	Crohn's Disease
CPF:	Complex Perianal Fistula
CRF:	Case Report Form
CRO:	Contract Research Organisation
GCP:	Good Clinical Practice
GPP:	Good Pharmacoepidemiology Practices
IBD:	Inflammatory Bowel Disease
IBDQ:	Inflammatory Bowel Disease Questionnaire
ICH:	International Conference on Harmonisation
IEC:	Independent Ethics Committee
IRB:	Institutional Review Board
LIFT:	Ligation of the Intersphincteric fistula tract
MCS:	Mental Component Score
PDAI:	Perianal Disease Activity Index
PCS:	Physical Component Score
QoL:	Quality of Life
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SADR:	Serious Adverse Drug Reaction
TNF:	Tumor Necrosis Factor
WPAI:	Work Productivity and Activity Impairment

2 Introduction

Crohn's disease (CD) is a life-long chronic inflammatory condition of the gastrointestinal tract, resulting from an interaction between environmental and genetic factors (1,2). This disease is frequently complicated by fistulas, which may form between segments of the intestine and the skin or adjacent organs (e.g., bladder or vagina) (3).

Fistulas may be classified as either simple or complex. According to the American Gastroenterological Association (AGA), a simple fistula is low (superficial or low intersphincteric or low transsphincteric origin of the fistula tract), has a single external opening, has no pain or fluctuation suggesting perianal abscess, and has no evidence of a rectovaginal fistula and anorectal stricture. A complex fistula is high (high intersphincteric or high transsphincteric or extrasphincteric or suprasphincteric origin of the fistula tract), may have multiple external openings, may be associated with the presence of pain or fluctuation to suggest a perianal abscess, and may be associated with the presence of a rectovaginal fistula, anorectal stricture or active rectal disease at endoscopy (4). Around 30% to 50% of CD patients present perianal fistulas (5), the majority of which (70-80%) are classified as complex (6,7).

The symptoms and complications of perianal fistulas, such as pain, scarring, discharge, fecal incontinence, and sexual difficulties, may lead to a considerable deterioration of the patients' Quality of Life (QoL) (5). Nonetheless, a recent systematic review showed that published studies on the QoL of CD patients with complex perianal fistulas (CPFs) are lacking in Europe (8). Indeed, only one study assessing QoL was identified, which showed that patients with perianal CD (84% of whom had complex anal fistulas) who underwent surgical treatment had significantly lower Inflammatory Bowel Disease Questionnaire (IBDQ) and physical health scores on the SF-12 in comparison with healthy controls. However, no differences in SF-12 mental health scores were observed (9). Similarly, only one study reporting data on the costs resulting from the management of CPF in CD patients was identified. This study, conducted in Spain, concluded that CD patients with fistulas account for a large part of the overall burden and economic costs of this disease (10). Accordingly, a study performed in the United States in 2008 reported that direct costs were significantly higher among fistulizing CD patients versus those without fistulas ($35373 vs $15564 per patient per year, respectively; $p<0.0001$) (11). Still, as both these studies considered direct costs only, the total cost of CPF among patients with CD is expected to have been underestimated (8). Indirect costs,

such as those resulting from work absenteeism and sick leave, have rarely been considered in studies evaluating the burden of complex perianal CD (2).

Though the burden of CPFs has seldom been studied, perianal disease (including fistulas, fissures, abscesses and stenosis) has been shown to significantly impact the QoL and sexual function of Inflammatory Bowel Disease (IBD) patients (12). Indeed, a study comparing IBD patients (including CD and ulcerative colitis) with and without perianal disease reported significantly lower SF-36 scores on all subscales – physical functioning, limitations due to physical health and emotional problems, energy/fatigue, emotional well-being, social functioning and general health – among the latter. Moreover, more than two-thirds of patients with perianal disease reported restriction of sexual activities (slight restriction [28%], moderate limitations [25%], marked limitations [12%], unable to engage in sexual activities [4%]). Patients with perianal disease were also more likely to report sick leave in the last 6 months and the influence of IBD on work productivity during the last 6 months was also significantly higher.

Treatment of perianal fistulas is aimed at promoting long-term fistula healing while preserving continence and preventing diverting stomas (13). However, the currently available therapies rarely allow to achieve these goals, particularly among patients with complex fistulas (14). Available treatments for complex fistulas include antibiotics, immunosuppressants, monoclonal antibodies (Tumor Necrosis Factor [TNF]-inhibitors), and surgery (namely fistulotomy, advancement flap, ligation of the intersphincteric fistula tract [LIFT], fibrin glue, anal fistula plug, and seton placement) (4,15,16). Complex fistulas are specially challenging to treat as they are exceptionally refractory to conventional therapies (such as immunomodulators and antibiotics) and anti-TNFs (17–19). Additionally, only a small proportion of patients achieve long-term remission (20), with 60% to 70% relapsing after stopping treatment (21–23).

Rationale

As stated above, there is a lack of data regarding the burden of CPFs among patients with CD. To the best of our knowledge, no study assessing QoL, sexual function, and healthcare resource consumption in this population has been conducted and published in Portugal. The present study will aim at bridging this data gap, by evaluating and characterizing these dimensions in CD patients with CPFs attending routine clinical practice in Portugal.

3 Study Objective(s) and Endpoint(s)/Outcome(s)

3.1 Objective(s)

The aim of this study is to characterize the QoL (general and IBD-specific), sexual function, work productivity and activity impairment, and healthcare resource utilization among CD patients with CPFs attending secondary care services (gastroenterology appointments) in Portugal.

3.1.1 Primary Objective

1) To assess the general QoL among CD patients with CPFs attending secondary care services in Portugal.

3.1.2 Secondary Objective(s)

1) To assess the IBD-specific QoL among CD patients with CPFs.
2) To assess the sexual function among CD patients with CPFs.
3) To assess fecal incontinence among CD patients with CPFs.
4) To assess the work productivity and activity impairment among CD patients with CPFs.
5) To assess the healthcare resource utilization in CD patients with CPFs within the three years prior to the inclusion visit.
6) To describe the sociodemographic, anthropometric, and clinical characteristics of CD patients with CPFs.
7) To describe the pharmacological and surgical treatments used for the management of CPFs within the three years prior to the inclusion visit.
8) To explore the association between general QoL and the sociodemographic, anthropometric, and clinical characteristics of CD patients with CPFs.

3.1.3 Exploratory Objective(s)

1) To explore the association between IBD-specific QoL/sexual function and the sociodemographic, anthropometric, and clinical characteristics of CD patients with CPFs.

3.2 Endpoint(s)/Outcome(s)

3.2.1 Primary Endpoint

1) Meta-scores of the SF-12 questionnaire (physical component score [PCS-12] and mental component score [MCS-12]).

3.2.2 Secondary Endpoint(s)

1) Short IBDQ (SIBDQ) questionnaire score.
2) SQOL-M and SQOL-F questionnaire scores for male and female patients, respectively.
3) Wexner score.
4) Work Productivity and Activity Impairment (WPAI) questionnaire score.
5) Outpatient visits (gastroenterology or other medical specialty), emergency room visits, hospitalizations (≥24 hours), and pharmacological and surgical treatments used for the management of CPFs within the three years prior to the inclusion visit.
6) Patients' sociodemographic, anthropometric and clinical characteristics.
7) Pharmacological and surgical treatments used for the management of CPFs within the three years prior to the inclusion visit.
8) Association between general QoL (PCS-12 and MCS-12) and the patients' socio-demographic, anthropometric and clinical characteristics.

3.2.3 Exploratory Endpoint(s)

1) Association between IBD-specific QoL (SIBDQ score)/sexual function (SQOL-M and SQOL-F scores) and the patients' socio-demographic, anthropometric and clinical characteristics.

4 Study Methods

4.1 Study Schedule

Planned Start of the Study: April 2021

Planned collection of first patient data (first patient first visit): April 2021

Planned End of Study (last patient last visit): December 2021

Date of database lock: February 2022

The appointed Contract Research Organisation (CRO) will ensure that End-of-Study notification is submitted to the concerned authorities and IEC/IRB for each site and for the complete study, as locally required.

Takeda Portugal will ensure that results are made publicly available as required by local authorities.

Based on upcoming knowledge, the Takeda Portugal might choose to terminate the study prematurely. In such case study sites, IECs/IRBs and authorities will be informed promptly.

4.2 Study Design

This is a national, observational, cross-sectional study primarily aimed at assessing the general QoL among CD patients with CPFs in the Portuguese routine clinical practice. In addition to the cross-sectional design, the study will have a retrospective component to collect data on healthcare resource utilization and on the pharmacological and surgical treatments used for the management of CPFs in the three years prior to the inclusion visit.

This study is a 'non-interventional study' as defined in Directive 2001/20/EC and will follow the guidelines for GPP. This means that:

- The assignment of a subject to a particular therapeutic strategy is not decided in advance by the study protocol but falls within current practice.
- No additional diagnostic or monitoring procedures shall be applied to the patients.
- Epidemiological methods shall be used for the analysis of collected data.

The study will be conducted in five Portuguese public hospitals experienced in the management of patients with CD. Gastroenterologists working at the participating

hospitals will participate in the study as investigators. Eligible patients (i.e., meeting all inclusion criteria and no exclusion criteria) will be consecutively enrolled during routine medical appointments at the participating hospitals. These will include male and female CD patients aged 18 or older with CPF(s). Eligible patients will be invited to participate in the study until a total of 80 patients are enrolled (see Section 9.3).

Data on the demographic, anthropometric and clinical characteristics of enrolled patients and on the pharmacological and surgical treatments used for CPF management will be collected based on medical records review and patient interviews during the inclusion visit. The interviews will aim to minimize the potential limitations associated with relying on medical records for data collection (see below in *Limitations of the study design*). Patient-reported questionnaires will be completed at this visit to characterize the patients' general and IBD-specific QoL (SF-12 and SIBDQ, respectively), sexual function (SQOL-M and SQOL-F), work productivity and activity impairment (WPAI), fecal incontinence (Wexner score), and severity of CD involving the perianal area (perianal disease activity index [PDAI]). Information on healthcare resource utilization related with CPF management in the previous three years will be obtained retrospectively from the medical records.

The patient recruitment and data collection will occur simultaneously, during an expected period of 9 months. This period may be extended to allow for the recruitment of the required study sample.

Limitation of the study design

Due to the observational design of this study and the reliance on medical records for data collection, there is the potential for incomplete or missing documentation, poorly recorded and absent information. Patient interviews will be conducted to minimize this limitation, by complementing/validating the medical records' data.

The consecutive inclusion of eligible patients during routine medical appointments at the study sites, as well as the fact that sites must keep a screening log documenting the reasons for non-eligibility of non-enrolled patients (see Section 4.3), is expected to minimize selection bias during the recruitment process. In turn, this is expected to contribute to an adequate representativeness of the study population, thus increasing the generalizability of the study results to the population of CD patients with CPFs being

followed and treated in the secondary care setting, in Portugal.

One of the study PROs (Wexner score), which will be used to characterize the patients' fecal incontinence, is not validated for Portuguese language (Portugal). A process of translation/back-translation will be carried out prior to using this score in the study.

4.3 Selection of Study Population

Eligible patients include male and female CD patients aged 18 or older with CPF(s). A screening log will be kept at the study sites and will be updated as patients attend routine medical appointments. The date of signed informed consent (for included patients) and the reasons for non-enrolment (for excluded patients) should be documented in this log.

4.3.1 Inclusion Criteria

Subject eligibility is determined according to the following criteria prior to study inclusion:

1. Male or female patients aged 18 years or older at the inclusion visit.
2. Patients diagnosed with CD.
3. Presence of CPF(s), defined as ≥1of the following criteria:
    - high intersphincteric, high transsphincteric, extrasphincteric, or suprasphincteric location;
    - ≥2 external openings;
    - associated collections.
4. Patients attending routine gastroenterology appointments at the participating hospitals.
5. Patients capable of understanding and complying with protocol requirements, in the investigator's opinion.
6. Patients or, when applicable, the patients' legally acceptable representative, who signed and dated a written informed consent form and any required privacy authorization prior to the initiation of any study procedures.

4.3.2 Exclusion Criteria

Any patient who meets any of the following criteria will not qualify for study inclusion:

1. Patients diagnosed with ulcerative colitis or indeterminate IBD.
2. Patients with non-complex fistulas or with fistulas types other than perianal (e.g., rectovaginal).
3. Patients currently participating in any interventional clinical trial.

Patients should be included in the study only once.

Data erroneously collected from patients for whom written consent is not available, will not be included in or will be deleted from the database.

4.4 Treatments

Non-interventional/observational – no treatments/pharmacotherapy are instructed by the study protocol.

4.5 Premature Termination or Suspension of Study or Study Site

4.5.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless there is a significant violation of Good Clinical Practice (GCP/GPV) that compromises the ability to achieve the primary study objectives. In this case, a temporary suspension or early termination of the study may be required.

4.5.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP/GPP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

4.5.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that Takeda Portugal, an IRB/ IEC or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by Takeda Portugal or by the appointed Contract Research Organisation (CRO); the procedure will be followed by applicable study sites during the course of termination or study suspension.

4.6 Study Plan

The data to be collected for each enrolled patient is summarized in Table 1 and described below.

Table 1 – Overview of study data

	Inclusion visit	Retrospective data collection
Informed consent	X	
Inclusion/exclusion criteria	X	
Sociodemographic and anthropometric characteristics	X	
Employment status	X	
Smoking status	X	
Date of CD diagnosis	X	
Date of CPF diagnosis	X	
Extraintestinal manifestations of CD	X	
Montreal classification for CD	X	
Harvey-Bradshaw Index (HBI)	X	
Perianal disease activity index (PDAI)	X	
Fistula characteristics	X	
Other perianal lesions	X	
Patient-reported questionnaires	X	
Pharmacological and surgical treatments for CPF		X[a]
Healthcare resource utilization		X[a]

[a]Within the three years prior to the inclusion visit

Study variables

The variables described below will be collected for each enrolled patient.

Patient characteristics

- Sociodemographic and anthropometric characteristics
  - Age
  - Sex
  - Height
  - Weight
  - BMI
- Employment status
  - Employed
  - Unemployed

  - Retired
  - Student
  - Other
- Smoking status
  - Current
  - Former
  - Never
- Date of CD diagnosis
- Date of CPF diagnosis (for each CPF presented by the patient at the inclusion visit)

Clinical characteristics

- Extraintestinal manifestation of CD
  - Arthralgia
  - Arthritis
  - Aphthous stomatitis
  - Sacroiliitis
  - Episcleritis
  - Erythema nodosum
  - Psoriasis
  - Sclerosing cholangitis
  - Ankylosing spondylitis
  - Pyoderma gangrenosum
  - Uveitis
  - Arthrosis/osteoarthritis
  - Hepatitis
  - Other
- CD characteristics
  - Montreal classification for CD
    - Age at onset
      - A1: at or below 16 years
      - A2: between 17 and 40 years
      - A3: above 40 years

- Disease location
  - L1 (terminal ileum)
  - L2 (colon)
  - L3 (ileocolon)
  - L4 (upper gastrointestinal [GI])
  - L1 + L4 (terminal ileum + upper GI)
  - L2 + L4 (colon + upper GI)
  - L3 + L4 (ileocolon + upper GI)
- Disease behavior
  - B1p (nonstricturing, nonpenetrating + perianal)
  - B2p (stricturing + perianal)
  - B3p (penetrating + perianal)

- Disease activity (Harvey-Bradshaw Index [HBI])

- PDAI
- Fistula characteristics (for each CPF presented by the patient at the inclusion visit)
  - Fistula type
    - High intersphincteric
    - High transsphincteric
    - Suprasphincteric
    - Extrasphincteric
    - Other
  - Number of internal fistula openings
  - Number of external fistula openings
  - Fistula position (midline vs. lateral)
  - Presence of seton (yes/no). If yes, date of seton placement
- Other perianal lesions
  - Skin tags
  - Hemorrhoids
  - Anal fissure
  - Anal ulcer
  - Perianal abscess
  - Anorectal stricture
  - Cancer

- Other

Study questionnaires

The following patient-reported questionnaires will be completed by the patients at the inclusion visit:

- SF-12 (for general QoL)
- SIBDQ (for IBD-specific QoL)
- SQOL-M and SQOL-F (for sexual function in male and female patients, respectively)
- WPAI (for work productivity and activity impairment)
- Wexner score

Pharmacological and surgical treatments for CPF management

At the inclusion visit, patients will be classified as treatment-naïve or treatment-experienced based on whether they have received any pharmacological treatment for CPF management since the diagnosis of this condition. Similarly, patients will be classified as surgery-naïve or patients who have underwent surgery for CPF management.

Moreover, the pharmacological and surgical treatments used for the management of CPF within the three years prior to the inclusion visit will be recorded. The start and end dates (when applicable) for pharmacological treatments and the date of surgery for surgical procedures will be collected.

- Pharmacological treatments
  - Antibiotics
    - Ciprofloxacin
    - Metronidazole
    - Other
  - Monoclonal antibodies
    - Infliximab
    - Adalimumab
    - Ustekinumab

    - Vedolizumab
    - Other
  - Immunosuppressants
    - Azathioprine
    - Mercaptopurine
    - Other
- Surgical treatments
  - Fistulotomy
  - Advancement flap
  - Ligation of the intersphincteric fistula tract (LIFT)
  - Fibrin glue
  - Anal fistula plug
  - Defunctioning stoma
  - Seton (cutting)
  - Seton (loose)
  - Other

Healthcare resource utilization

Data on healthcare resource utilization (HCRU) associated with CPF management within the three years prior to the inclusion visit will be collected. These data will include:

- Gastroenterology and other medical specialty appointments for the management of CPF
- Emergency room visits due to CPF
- Hospitalizations (≥24 hours) due to CPF:
  - Date of admission
  - Date of hospital discharge
  - ICU admission (yes/no). If yes: date of ICU admission/discharge

5 Study Administrative Structure

5.1 Study Sites

The study is planned to be conducted in five Portuguese sites (public hospitals) experienced in the management of CD patients. Gastroenterologists working at the participating hospitals will be invited to participate in the study as investigators.

Takeda Portugal or the appointed CRO will keep a record of the individuals responsible for each participating Study Site, the Site Responsibles.

5.2 Sponsor Personnel

Takeda Portugal will keep a record of all relevant sponsor personnel.

5.3 Contract Research Organisation (CRO)

A Contract Research Organisation (CRO) – CTI Clinical Trial & Consulting Services – will be responsible for the following tasks:

- Start-up activities (including regulatory submissions)
- Study monitoring
- Data management
- End of study notification
- Statistical analysis
- Final study report
- Study publications

The CRO will keep a record of all involved CRO personnel.

6 Ethics

This observational study will have no impact on the subject except for collection of informed consent to use the subject's data and for the completion of five patient-reported questionnaires. Patient-reported questionnaires will be completed during a single routine medical appointment (inclusion visit) at the participating hospitals to minimize the impact on the patients' routine clinical practice. The patient's participation in the study will last the duration of the routine medical appointment only.

6.1 Ethical conduct of the Study

This study will be conducted in accordance with the protocol, the current version of the Declaration of Helsinki, International Conference on Harmonisation E6 Good Clinical Practice, Good Pharmacoepidemiology Practices (GPP), ISPE GPP guideline and any local regulations. Special attention will be paid to data protection, considering the EU General Data Protection Regulation (95/46 EC) and applicable Portuguese legislation, namely law No. 58/2019.

Takeda Portugal and/or the appointed CRO will ensure that the protocol, any amendments and the Subject Information Sheet/Informed Consent Form are submitted to the relevant Independent Ethics Committees (IECs)/Institutional Review Boards (IRBs) according to local requirements.

Takeda Portugal is responsible for meeting the International Conference on Harmonisation (ICH) requirement for yearly updates to the IECs/IRBs, if applicable.

6.2 Independent Ethics Committee / Institutional Review Board and Authorities IEC/ IRB

According to applicable regulations, the appointed CRO or the Site Study Responsible will:

- notify or obtain approval from the relevant IEC/IRB of the protocol, any amendments and the Subject Information Sheet / Informed Consent Form

The appointed CRO or the Study Responsible will submit required documents to the IEC / IRB, such as:

- periodic updates on the progress of the study
- notification of the end-of-study
- a summary of the study results

Takeda Portugal or the appointed CRO will keep an updated list of all submission and approval dates of all documents submitted to the IEC / IRB and will provide the Site Responsible with a copy of this list. Copies of the documents will be distributed upon request.

6.3 Authorities

Takeda Portugal or the appointed CRO will send required documents to the competent authority (CA) and/or other national or regional authorities. Takeda Portugal or the appointed CRO will keep an updated list of submission and approval dates and a copy of all documents submitted.

6.4 Subject Information and Written Informed Consent

The Site Study Responsible must give the subject (and if applicable, parent or legal guardian) oral and written information about the study in a form that the subject (and if applicable, the parent or legal guardian) can understand, and obtain the subject's (and if applicable, the subject's assent and the parent's or legal guardian's) written consent before collection of identifiable subject information (hereinafter referred to as personal data). Before consenting, the subject (and if applicable, parent or legal guardian) must be left with ample time to consider and to pose questions. Since the study is observational the consent only concerns the data collection per se and is not consent to any interventional procedure or treatment. Moreover, as patient-reported questionnaires that are not part of routine clinical practice will be used, the ICF will briefly explain what each questionnaire is aimed at assessing and will clearly state that participation in the study is associated with the completion of such questionnaires.

The subject must agree that Takeda Portugal personnel, appointed CRO personnel, or IEC/IRB or CA personnel (national or other) may require direct access to the subject's data / personal records which were collected, processed and stored in an anonymous form.

The subject must agree that his / her data will be processed and stored in an anonymous form for evaluation of this study and any later overviews. Data may also be transferred in anonymous form to third parties, e.g., to other companies or authorities, that may be located in other countries with potentially different regulations for data.

The subject and subject's parent or legal guardian, if applicable, has the right to withdraw his/her consent at any time without prejudice. In the Informed Consent Form, it is stated that

if consent is withdrawn, any data collected before withdrawal of consent will be kept. One original signed Informed Consent Form must be kept at the study site, and one is provided to the subject and/or subject's parent or legal guardian, as applicable.

For details, see the Subject Information Sheet and Informed Consent Form.

7 Safety Reporting

This is an observational study, where patients will not receive any study medication.

7.1 Definitions

Adverse Event

An adverse event (AE) is any untoward medical occurrence in a subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, a new disease or worsening in severity or frequency of a concomitant disease, temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Although abnormal laboratory values are typically not considered AEs, the following considerations may result in an abnormal laboratory value being considered an AE:

- A laboratory test result that meets the criteria for an SAE
- A laboratory test result that requires the subject/patient to receive specific corrective therapy
- A laboratory abnormality that leads to discontinuation of therapy
- A laboratory abnormality that the health care provider considers to be clinically significant

Serious Adverse Events

A Serious Adverse Event (SAE) is any untoward medical occurrence that at any dose:

- Results in death. Note that death is an outcome of an event. The event(s) causing death should be recorded.
- In the view of the Health care provider, places the subject/patient at immediate risk of death (a life threatening event); however, this does not include an event that, had it occurred in a more severe form, might have caused death
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Results in a congenital anomaly/birth defect

- An SAE may also be any other medically important event that, in the opinion of the Health care provider, may jeopardize the subject/patient or may require intervention to prevent one of the other outcomes listed in the definition above. (Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or convulsions occurring at home that do not require an inpatient hospitalization.)

Adverse Drug Reactions

An adverse drug reaction (ADR) is an AE for which there is at least a reasonable suspicion of a causal relationship between an AE and a suspected medicinal product.

Product Quality Issues

A Product Quality Issue (PQI) refers to defects related to the safety, identity, strength, quality, or purity of the product or with the physical characteristics, packaging, labeling, or design of the product.

Special Situation Reports

A Special Situation Report (SSR) includes any of the following events:

- Pregnancy: Any case in which a pregnancy patient is exposed to a Takeda Product or in which a female patient or female partner of a male patient becomes pregnant following treatment with Takeda Product. Exposure is considered either through maternal exposure or via semen following paternal exposure.
- Breastfeeding: Infant exposure from breast milk
- Overdose: All information of any accidental or intentional overdose
- Drug abuse, misuse or medication error: All information on medicinal product abuse, misuse or medication error (potential or actual)
- Suspected transmission of an infectious agent: Suspected (in the sense of confirmed or potential) transmission of an infectious agent by a medicinal product.
- Lack of efficacy of Takeda Product
- Accidental/Occupational exposure
- Use outside the terms of the marketing authorization, also known as “off-label”

- Use of falsified medicinal product
- Drug-drug interactions and drug-food interactions
- Inadvertent or accidental exposure with or without an AE
- Unintended benefit

A SSR should be reported even if there is no associated AE.

7.2 Safety events spontaneously notified to the investigator(s) or research team

If during the conduct of the study the investigator(s) or a member of the research team is spontaneously informed by a healthcare professional or patient of an SAE, AE, ADR, SSR or PQI where the event/issue pertains to a Takeda product (or unbranded generic), such information should be notified to the relevant Takeda Pharmacovigilance department within 1 working day for fatal or life-threatening SAEs, within 4 calendar days for other SAEs, and within 7 calendar days for all other events. As such reports are spontaneously notified, causality of any adverse events should be assumed unless there is evidence to the contrary.

Takeda Contact Information

Spontaneous reports are notified to the local Pharmacovigilance department, according to the timelines described above from reception through the email address AE.PRT@takeda.com.

8 Data Quality Control and Assurance

8.1 Quality Control

Monitoring visits will be conducted during the study to ensure that all data have been accurately and completely recorded in the case report forms (CRFs). Electronic database entries will be compared against the source documents (e.g. hospital medical records). The study monitor should have direct access to all relevant source documents. The investigator should provide and monitor the access to this information and take the necessary measures to correct any data that is not completed as per the protocol.

The investigator is responsible for ensuring that the study is conducted according to the study protocol and for recording any occurrence that may be considered as a protocol deviation. Study monitors should also record all protocol deviations identified.

All study data will be entered in an electronic database. The database will have automatic controls in place to limit errors during the data entry process.

8.2 Audit from Quality Assurance Unit

The Quality Assurance (QA) unit may audit the study to ensure that study procedures comply with the protocol and standard operating procedures, and that collected data is correct and complete.

8.3 Inspection by IRB/IEC or Competent Authority

Representatives from IRB/IEC or CA may in rare cases wish to inspect the study on site. Upon receiving notification of such inspection, the Study Site Responsible must immediately contact Takeda Portugal and must make the records available as requested.

8.4 Data Management

Data Management will be carried out by the contracted CRO (CTI) according to a Data Management Plan, which must be written and approved before the design of the study database is finalized. The data management provider should approve all data formats before the data collection tools are made available to the sites.

If the written informed consent of a subject is known not to be available in spite of it being required, data for this subject is not entered into or is deleted from the database.

If a subject is erroneously included in the study more than once only the data relating to the

first inclusion will be kept in the database and be available for analysis. Data from later inclusions will be transferred to the first dataset when relevant, i.e. if collected within the time frame of the first follow-up period.

The current Standard Coding Instructions for coding of medical history, concomitant illness (MedDRA), and concomitant medication (WHO-Drug) must be followed.

Each patient will receive a unique identification code that will be used to identify her/him throughout the data collection and statistical analysis, and that must be used on all study documentation related to that patient. Once assigned to a patient, the identification code will not be reused. The identification number will consist of five digits: the first two corresponding to the study site number and the last three a sequential number starting at 001). For instance, the identification number of the fourth subject of site 03 will be 03004.

8.4.1 Data Collection Tools and Flow

The Study Site will receive data collection tools (CRFs, access to electronic data capture, etc.) from Takeda Portugal or the appointed CRO. Whenever possible, complete data sets should be entered. Text field entries and any data collected on paper should be legible and follow the CRF completion guide.

Following informed consent signature, the data required per protocol will be collected by the investigator or designee and entered in the study database. Study data will be collected based on medical records review, patient interviews and patient-reported questionnaires applied at the inclusion visit.

The Study Site Responsible must sign off the complete data set for each subject, confirming the collected data.

No adverse events will be collected or analyzed as part of this study as there are not safety endpoints. This non-interventional study is not designed to identify or quantify safety issues related in any way with Takeda products. Only SAEs, AEs, ADRs, SSRs and PQIs spontaneously reported to the investigator(s) or research team will be communicated to Takeda according to Section 7.

When the database has been declared to be complete and accurate, it will be locked and made available for statistical analysis. Any changes to the database after this time can only be made after agreement from Takeda Portugal and must be documented.

9 Statistical Methods and Determination of Sample Size

Statistical analysis will be performed by the CRO's biostatistics team according to a Statistical Analysis Plan (SAP) to be developed separately from the protocol.

This section/the Statistical Analysis Plan describes the statistical analyses as foreseen at the time of planning the study. Any known deviations from the planned analyses, the reason for such deviations and all alternative / additional statistical analyses performed must be documented and described in subsequent study documents, namely the Statistical Report and Clinical Study Report.

9.1 Statistical Analysis Plan

9.1.1 General considerations

This study is observational and epidemiological methods will be employed for data analyses.

All quantitative variables will be summarized using descriptive statistics, namely mean, standard deviation, median, range (minimum and maximum values) and interquartile ranges. All qualitative variables will be summarized by absolute (n) and relative (%) frequencies. The statistical analysis will be performed through frequency tables for qualitative variables and tables with descriptive statistics for quantitative variables.

No imputation of missing data will be performed. Percentages will be calculated based on non-missing values.

All eligible patients (i.e., meeting all inclusion criteria and no exclusion criteria) will be considered for the statistical analyses.

All statistical procedures will be performed with the software SAS 9.4 or higher.

For details of the statistical analyses please refer to the Statistical Analysis Plan.

9.1.2 Primary analysis

To characterize the patients' general QoL, the results obtained for each item of the SF-12 will be summarized in a frequency table, including counts (n) and percentages (%). The two resulting meta-scores – the physical health composite scale score and the mental health composite scale score – will be summarized by descriptive statistics, namely mean (with 95% CI), standard deviation, median, range (minimum and maximum values) and interquartile ranges.

Ninety-five per cent CIs will be determined for the mean meta-scores of the SF-12 according to the following formula:

$$\text{mean} \pm 1.96 \times \frac{\text{standard deviation}}{\sqrt{n}}$$

9.1.3 Secondary analyses

IBD-specific QoL

To characterize the patients' IBD-specific QoL, the results obtained for each item of the SIBDQ and the overall score will be summarized will be summarized by descriptive statistics, namely mean, standard deviation, median, range (minimum and maximum values) and interquartile ranges.

Sexual function

The results obtained for each of the 11 items included in the SQOL-M questionnaire (for male patients) will be summarized in a frequency table, including counts (n) and percentages (%), and by descriptive statistics, namely mean, standard deviation, median, range (minimum and maximum values) and interquartile ranges. The overall score will also be summarized descriptively.

The results obtained in each of the 18 items included in the SQOL-F (for female patients) will be summarized in a frequency table, including counts (n) and percentages (%), and by descriptive statistics, namely mean, standard deviation, median, range (minimum and maximum values) and interquartile ranges. The overall score will also be summarized descriptively.

Fecal incontinence

The results obtained for each of the five items of the Wexner score will be summarized in a frequency table, including counts (n) and percentages (%). The overall score will be summarized by descriptive statistics, namely mean, standard deviation, median, range (minimum and maximum values) and interquartile ranges.

Impact on social/work activities and work productivity

Results from the first question of the WPAI will be summarized by counts (n) and percentages (%). Data on the remaining six questions will be summarized by descriptive statistics, namely mean, standard deviation, median, range (minimum and maximum values) and interquartile ranges. Moreover, the scores obtained for the four domains assessed by the WPAI – absenteeism (work time missed), presenteeism (impairment at work / reduced on-the-job effectiveness), work productivity loss and activity impairment – will be summarized descriptively.

Healthcare Resource Utilization

Data on outpatient visits (number, medical specialty), emergency room visits (number), hospitalizations ≥24 hours (number, length of stay, ICU admission, ICU length of stay), and pharmacological and surgical treatments used for CPF management (number) within the three years prior to the inclusion visit will be summarized descriptive statistics – namely mean, standard deviation, median, range (minimum and maximum) and interquartile ranges – or by absolute (n) and relative (%) frequencies, as applicable.

Moreover, the number of patients with at least one outpatient visit, emergency room visit, and hospitalization ≥24 hours will be presented.

Patients' characteristics

All patients sociodemographic, anthropometric and clinical characteristics described in Section 4.6 will be summarized by descriptive statistics – namely mean, standard deviation, median, range (minimum and maximum) and interquartile ranges – or by absolute (n) and relative (%) frequencies, as applicable. The classification of patients as treatment- and/or surgery-naïve will also be presented by descriptive statistics.

Patients will be divided into three categories based on the timing of CPF diagnosis in relation to the CD diagnosis:

- Prior to CD diagnosis
- At CD presentation (i.e., when CPF was diagnosed in the same year as CD)
- During the course of the disease

Based on the HBI score, patients will be categorized into four categories:

- Remission (score <5)
- Mild activity (5-7)
- Moderate activity (8-16)
- Severe activity (>16)

Based on the PDAI score, patients will be divided into two groups (24):

- Inactive fistulizing disease (≤4)
- Active fistulizing disease (>4)

Pharmacological treatments and surgeries for CPF

The pharmacological and surgical treatments used for the management of CPF (see Section 4.6) will be described by counts (n) and percentages (%).

For each pharmacological treatment (antibiotics, monoclonal antibodies and immunosuppressants), patients will be divided into three categories (current users, past users, and non-users) considering the three years prior to the inclusion visit. For instance, for immunosuppressants, the proportions of patients using these drugs at the inclusion visit, those who have used them within the last three years, and those who have not used them in this period will be summarized.

Current combinations (i.e., combinations used by the patient at the inclusion visit) will be described by counts (n) and percentages (%).

Factors associated with general QoL (SF-12)

Bivariate analysis

Comparisons of general QoL (for the two SF-12 meta-scores – PHC and MHC) and between groups defined based on qualitative variables, of patient characteristics, will be tested with the t-test for independent samples/ANOVA for two/three or more independent samples or with the Mann-Whitney/Kruskal-Wallis non-parametric tests, according to the assumption validations of the statistical test. The following qualitative variables will be considered for the bivariate analysis: sex, smoking status, employment status, extraintestinal manifestations of Crohn's

disease, Montreal classification for CD disease (age at onset, disease location, and disease behavior), fistula type and position, CD disease activity (remission, mild activity, moderate activity, and severe activity), treatment-naïve (yes/no), surgery-naïve (yes/no), treatment- and surgery-naïve (yes/no), surgery for the management of CPFs within the three years prior to the inclusion visit (yes/no), type of surgery, and presence of seton, perianal abscess and anorectal stricture.

Associations between general QoL (for PHC and MHC) and quantitative variables of patient characteristics, will be performed through Pearson correlation coefficient or Spearman correlation coefficient (in case the normality assumption is not verified). The following quantitative variables will be considered for the bivariate analysis: age, BMI, time since CD diagnosis, number of CPFs presented at the inclusion visit, time since CPF diagnosis (in patients with more than one CPF at the inclusion visit, the oldest date of diagnosis will be considered), PDAI score, number of internal and external fistula openings, time since seton placement, SIBDQ score, SQOL-M score (for male patients) and SQOL-F score (for female patients), and Wexner score.

Linear multiple regressions

Moreover, linear multiple regressions will be used to explore the association between the dependent variable (PCS and MCS meta-scores of the SF-12) and independent variables of interest according to the bivariate analysis results. Regression coefficients (B) and 95% confidence intervals will be computed to measure the magnitude of these associations.

9.1.4 Exploratory analyses

The same methodology described in Section 9.1.3 (for factors associated with general QoL [SF-12]) will be followed to explore the association between independent variables of interest and the following dependent variables:

- IBD-specific QoL (SIBDQ score)
- Sexual function (SQOL-M and SQOL-F scores for male and female patients, respectively)

9.2 Interim Analyses

No interim analyses are planned for this study.

9.3 Determination of Sample Size

The sample size was determined based on the study's primary objective – to assess the general QoL of CD patients with CPF.

To determine the sample size, an expected standard deviation of the outcome (SF-12 score) is required. Ideally, a standard deviation of the SF-12 score assessed in CD patients with CPFs should be used. However, we found no studies in the literature reporting SF-12 scores exclusively for CD patients with CPFs. Alternatively, we used the data reported by a study that evaluated the QoL via SF-12 in CD patients (25). This study reported mean scores of 49.1 (±10.2) and 49.6 (±10.6) for PCS-12 and MCS-12, respectively.

Considering an expected standard deviation of 10.6 (the most conservative) based on the abovementioned study, a confidence level at 95% and a margin of error of approximately 2.3, a total of 80 patients should be included in the study to assess the general QoL via the SF-12 questionnaire. The formula below was used for the sample size determination:

$$n = \frac{z^2 \times s^2}{m^2}$$

Where:

n = required sample size

z = confidence level at 95% (standard value of 1.96)

s = expected standard deviation

m = margin of error

10 Reports

The Final Study Report should be available within one year from collection of the last data point, and the participating sites should be informed about the results when the report is finalized.

11 Publication, Disclosure, and Clinical Trial Registration Policy

Takeda Portugal aims to have the results of this study published.

Takeda Portugal has the right to use the data and results for regulatory purposes and for internal presentation within the company and to partners.

Takeda may post the results of the study on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

12 Archiving of Study Documentation

During the course of the study the Site Responsible must as a minimum file the below essential documents in the Study Site File:

- Written agreement between Takeda Portugal or the appointed CRO and the Study Site.
- The study protocol and any amendments
- Signed and dated protocol agreement and amendment agreements, if any, with the original signature of the Site Responsible
- Subject Information Sheet and Informed Consent Form in local language (notified to / approved by Independent Ethics Committees (IECs) / Institutional Review Boards (IRBs) as locally required), including the original signed Forms
- The list of participating subjects
- Written IEC / IRB approval / vote according to local regulations
- The completed CRFs
- The progress reports

After final database lock the Site Responsible must as a minimum store the list of

participating subjects and the signed Informed Consent Forms on site for 5 years. The Site Responsible should store additional study documentation for a longer period of time as required by any local regulations and/or hospital requirement.

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14 Appendices

1. SF-12

A Sua Saúde e Bem-Estar

As perguntas que se seguem pedem-lhe sua opinião sobre a sua saúde. Esta informação nos ajudará a saber como se sente, e como é capaz de desempenhar as atividades habituais. ***Obrigado por responder a este questionário!***

Para cada uma das seguintes perguntas, por favor marque uma ☒ na caixa que melhor descreve sua resposta.

1. Em geral, diria que a sua saúde é:

Excelente	Muito boa	Boa	Razoável	Fraca
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

2. As perguntas que se seguem são sobre atividades que pode executar no seu dia-a-dia. Será que <u>a sua saúde atual o/a limita</u> nestas atividades? Se sim, quanto?

	Sim, muito limitado/a	Sim, um pouco limitado/a	Não, nada limitado/a
a <u>Atividades moderadas</u>, tais como deslocar uma mesa, aspirar a casa, andar de bicicleta, ou nadar	☐ 1	☐ 2	☐ 3
b Subir <u>vários</u> lanços de escada	☐ 1	☐ 2	☐ 3

3. Durante as <u>últimas 4 semanas</u>, quanto tempo teve no seu trabalho ou outras atividades diárias regulares algum dos problemas apresentados a seguir <u>como consequência do seu estado de saúde físico</u>?

	Sempre	A maior parte do tempo	Algum tempo	Pouco tempo	Nunca
a <u>Realizou menos</u> do que queria	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Sentiu-se limitado/a no <u>tipo</u> de trabalho ou outras atividades	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

4. Durante as <u>últimas 4 semanas</u>, quanto tempo teve algum dos problemas apresentados a seguir com o seu trabalho ou outras atividades diárias regulares, <u>devido a quaisquer problemas emocionais</u> (tal como sentir-se deprimido/a ou ansioso/a)?

	Sempre	A maior parte do tempo	Algum tempo	Pouco tempo	Nunca
a <u>Realizou menos</u> do que queria	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Realizou o trabalho ou outras atividades de forma <u>menos cuidadosa que o habitual</u>	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

5. Durante as <u>últimas 4 semanas</u>, de que forma é que a <u>dor</u> interferiu com o seu trabalho normal (tanto o trabalho fora de casa como o trabalho doméstico)?

Absoluta-mente nada	Um pouco	Moderada-mente	Bastante	Imenso
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

6. As perguntas que se seguem pretendem avaliar a forma como se sentiu e como lhe correram as coisas durante as últimas 4 semanas. Para cada pergunta, por favor dê a resposta que melhor descreva a forma como se sentiu. Quanto tempo, durante as últimas 4 semanas...

	Sempre	A maior parte do tempo	Algum tempo	Pouco tempo	Nunca
a Se sentiu calmo/a e tranquilo/a?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
b Teve muita energia?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
c Se sentiu triste e deprimido/a?	☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

7. Durante as últimas 4 semanas, até que ponto é que a sua saúde física ou problemas emocionais limitaram a sua atividade social (tal como visitar amigos ou familiares próximos)?

Sempre	A maior parte do tempo	Algum tempo	Pouco tempo	Nunca
☐ 1	☐ 2	☐ 3	☐ 4	☐ 5

Obrigado por completar estas perguntas!

2. SQOL-M

Questionário sobre a Qualidade da Vida Sexual - Masculino© (Portuguese version of the SQoL-M)

Este questionário é composto por um conjunto de afirmações, cada uma sobre os pensamentos e sentimentos que eventualmente tenha em relação à sua vida sexual. A afirmação pode referir-se tanto a aspectos positivos como negativos da sua vida sexual. Este questionário destina-se a todos os homens, independentemente da sua escolha sexual.

Pedimos-lhe que classifique cada afirmação de acordo com o quanto concorda ou discorda com a mesma, pondo um círculo à volta de uma das seis respostas possíveis.

Ao responder a estas questões deve ter em conta as seguintes definições:

Vida sexual: refere-se tanto às actividades sexuais físicas como à relação sexual emocional que tem com a sua parceira.

Actividade sexual: inclui qualquer actividade que possa resultar em estimulação ou prazer sexual, por exemplo, relações sexuais, carícias, preliminares, masturbação (tanto auto-masturbação como a sua parceira a masturbá-lo a si) e sexo oral (ou seja, a sua parceira a fazer-lhe sexo oral).

Normalmente a primeira resposta que lhe vem à cabeça é a melhor; por isso, não passe muito tempo com cada pergunta.

Todas as suas respostas serão totalmente confidenciais

	Concordo completa-mente	Concordo moderada-mente	Concordo ligeiramente	Discordo ligeira-mente	Discordo moderada-mente	Discordo completa-mente
1. Quando penso na minha vida sexual, sinto-me frustrado.						
2. Quando penso na minha vida sexual, sinto-me deprimido.						
3. Quando penso na minha vida sexual, sinto-me menos homen.						
4. Perdi confiança em mim mesmo como parceiro sexual.						
5. Quando penso na minha vida sexual, sinto-me ansioso.						
6. Quando penso na minha vida sexual, sinto-me zangado.						
7. Preocupo-me com o futuro da minha vida sexual.						
8. Quando penso na minha vida sexual, sinto-me embaraçado.						
9. Quando penso na minha vida sexual, sinto-me culpado.						
10. Quando penso na minha vida sexual, preocupo-me que a minha parceira se sinta magoada ou rejeitada.						
11. Quando penso na minha vida sexual, sinto-me como se tivesse perdido algo.						

SQoL-M: 29/10/99

Portuguese (Portugal), May 2004

3. SQOL-F

QUESTIONARIO SOBRE A QUALIDADE DE VIDA SEXUAL • FEMININO ©
{SQoI-F)

Este questionario e composto por um conjunto de afirma96es, cada uma sobre os pensamentos e sentimentos que eventualmente tenha em relai;ao a sua vida sexual. A afirmai;ao pode referir-se tanto a aspectos positivos corrio negativos da sua vida sexual. Este questionario destina-se a todas as mulheres, independentemente da sua escolha sexual.

Pedimos-lhe que classifique cada afirmai;ao de acordo com o quanto concorda ou discorda com a mesma, pondo um cfrculo a volta de urna das seis respostas possfveis.

Ao responder a estas quest6es deve ter em conta as seguintes defini96es:

Vida sexual: refere-se tanto as actividades sexuais fisicas como a relai;ao sexual emocional que tern com o seu companheiro.

Actividade sexual: inclui qualquer actividade que possa resultar em estimula9ao ou prazer sexual, por exemplo, rela96es sexuais, carfcias, preliminares, masturba9ao (tanto auto-masturba9ao como o seu companheiro a masturba-la a si) e sexo oral (ou seja, o seu companheiro a fazer-lhe sexo oral).

Normalmente a primeira resposta que lhe vem a cabei;a e a melhor; por isso, nao passe muito tempo com cada pergunta.

Todas as suas respostas serao totalmente confidenciais

QUESTIONARIO SOBRE A QUALIDADE DE VIDA SEXUAL - FEMININO © (SQoL-F)

D **(1) Not Done**

1. Quando penso na minha vida sexual, e uma parte agradavel da minha vida	Concordo completa-mente	Concordo moderada-mente	Concordo ligeiramente	Discordo ligeira-mente	Discordo moderada-mente	Discordo completa-mente
2. Quando penso na minha vida sexual, sinto-me frustrada	Concordo cornpleta-mente	Concordo moderada-mente	Concordo ligeiramente	Discordo ligeira-mente	Discordo moderada-mente	Discordo completa-mente
3. Quando penso na minha vida sexual, sinto-me deprimida	Concordo completa-mente	Concordo moderada-mente	Concordo ligeiramente	Discordo ligeira-mente	Discordo moderada-mente	Discordo completa-mente
4. Quando penso na minha vida sexual, sinto-me menos mulher	Concordo completa-mente	Concordo moderada-mente	Concordo ligeiramente	Discordo ligeira-mente	Discordo moderada-mente	Discordo completa-mente
5. Quando penso na minha vida sexual, sinto-me bem comigo pr6pria	Concordo completa-mente	Concordo moderada-mente	Concordo ligeiramente	Discordo ligeira-mente	Discordo moderada-mente	Discordo completa-mente
6. Perdi confianc;a em mim pr6pria como parceira sexual	Concordo completa-mente	Concordo moderada-mente	Concordo ligeiramente	Discordo ligeira-mente	Discordo moderada-mente	Discordo completa-mente
7. Quando penso na minha vida sexual, sinto-me ansiosa	Concordo completa-mente	Concordo moderada-mente	Concordo ligeiramente	Discordo ligeira-mente	Discordo moderada-mente	Discordo completa-mente
8. Quando penso na minha vida sexual, sinto-me zangada	Concordo completa-mente	Concordo moderada-mente	Concordo ligeiramente	Discordo ligeira-mente	Discordo moderada-mente	Discordo completa-mente
9. Quando penso na minha vida sexual, sinto-me pr6xima do meu companheiro	Concordo completa-mente	Concordo moderada-mente	Concordo ligeiramente	Discordo ligeira-mente	Discordo moderada-mente	Discordo completa-mente

QUESTIONARIO SOBRE A QUALIDADE DE VIDA SEXUAL - FEMININO© (SQoL-F)

10. Preocupo-me com o futuro da minha vida sexual	Concordo completa-mente	Concordo moderada-mente	Concordo ligeiramente	Discordo ligeira-mente	Discordo moderada-mente	Discordo completa-mente
11. Perdi o prazer na actividade sexual	Concordo completa-mente	Concordo moderada-mente	Concordo ligeiramente	Discordo ligeira-mente	Discordo moderada-mente	Discordo completa-mente
12. Quando penso na minha vida sexual, sinto-me embara9ada	Concordo completa-mente	Concordo moderada-mente	Concordo ligeiramente	Discordo ligeira-mente	Discordo moderada-mente	Discordo completa-mente
13. Quando penso na minha vida sexual, sinto que posso falar com o meu companheiro sobre assuntos sexuais	Concordo completa-mente	Concordo moderada-mente	Concordo ligeiramente	Discordo ligeira-mente	Discordo moderada-mente	Discordo completa-mente
14. Procuro evitar a actividade sexual	Concordo completa-mente	Concordo moderada-mente	Concordo ligeiramente	Discordo ligeira-mente	Discordo moderada-mente	Discordo completa-mente
15. Quando penso na minha vida sexual, sinto-me culpada	Concordo completa-mente	Concordo moderada-mente	Concordo ligeiramente	Discordo ligeira-mente	Discordo moderada-mente	Discordo completa-mente
16. Quando penso na minha vida sexual, preocupo-me que o meu companheiro se sinta magoado ou rejeitado	Concordo completa-mente	Concordo moderada-mente	Concordo ligeiramente	Discordo ligeira-mente	Discordo moderada-mente	Discordo completa-mente
17. Quando penso na minha vida sexual, sinto-me como se tivesse perdido algo	Concordo completa-mente	Concordo moderada-mente	Concordo ligeiramente	Discordo ligeira-mente	Discordo moderada-mente	Discordo completa-mente
18. Quando penso na minha vida sexual, estou satisfeita com a frequencia da actividade sexual	Concordo completa-mente	Concordo moderada-mente	Concordo ligeiramente	Discordo ligeira-mente	Discordo moderada-mente	Discordo completa-mente

Draft

4. SIBDQ

QUESTIONÁRIO SOBRE A QUALIDADE DE VIDA NA DOENÇA INFLAMATÓRIA INTESTINAL (SIBDQ)

Este questionário tem por objectivo avaliar como se tem sentido durante as últimas 2 semanas. Perguntar-se-á quais são os seus sintomas como consequência da doença inflamatória intestinal, como se sente em geral e qual tem sido a sua disposição.

1. Quantas vezes, durante as últimas 2 semanas, a sensação de fadiga ou cansaço e sentir-se enfraquecido têm sido para si um problema? Indique quantas vezes a fadiga ou o cansaço têm constituído para si um problema durante as últimas 2 semanas, escolhendo apenas uma resposta.

   ☐ 1 SEMPRE
   ☐ 2 QUASE SEMPRE
   ☐ 3 UMA BOA PARTE DO TEMPO
   ☐ 4 ALGUMAS VEZES
   ☐ 5 POUCAS VEZES
   ☐ 6 RARAMENTE
   ☐ 7 NUNCA

2. Quantas vezes, durante as últimas 2 semanas, teve de adiar ou desmarcar compromissos de ordem social devido ao problema intestinal? Assinale apenas uma resposta.

   ☐ 1 SEMPRE
   ☐ 2 QUASE SEMPRE
   ☐ 3 UMA BOA PARTE DO TEMPO
   ☐ 4 ALGUMAS VEZES
   ☐ 5 POUCAS VEZES
   ☐ 6 RARAMENTE
   ☐ 7 NUNCA

3. Qual o grau de dificuldade que teve, durante as últimas 2 semanas, em praticar desporto ou outras actividades de tempos livres que gostaria de ter realizado, em consequência do seu problema intestinal? Assinale apenas uma resposta.

   ☐ 1 ENORME DIFICULDADE; ACTIVIDADES IMPOSSÍVEIS DE PRATICAR
   ☐ 2 UMA GRANDE DIFICULDADE
   ☐ 3 MUITA DIFICULDADE
   ☐ 4 ALGUMA DIFICULDADE
   ☐ 5 UM POUCO DE DIFICULDADE
   ☐ 6 RARAMENTE SENTI DIFICULDADE
   ☐ 7 SEM DIFICULDADE; O PROBLEMA INTESTINAL NÃO AFECTOU A ACTIVIDADE DESPORTIVA OU AS ACTIVIDADES DE TEMPOS LIVRES

 Portuguese (Portugal)

4. Quantas vezes, durante as últimas 2 semanas, as dores no abdómen o perturbaram? Assinale apenas uma resposta.

- ☐ 1 SEMPRE
- ☐ 2 QUASE SEMPRE
- ☐ 3 UMA BOA PARTE DO TEMPO
- ☐ 4 ALGUMAS VEZES
- ☐ 5 POUCAS VEZES
- ☐ 6 RARAMENTE
- ☐ 7 NUNCA

5. Quantas vezes, durante as últimas 2 semanas, se sentiu deprimido ou desanimado? Assinale apenas uma resposta.

- ☐ 1 SEMPRE
- ☐ 2 QUASE SEMPRE
- ☐ 3 UMA BOA PARTE DO TEMPO
- ☐ 4 ALGUMAS VEZES
- ☐ 5 POUCAS VEZES
- ☐ 6 RARAMENTE
- ☐ 7 NUNCA

6. De um modo geral, quais os problemas que teve, durante as últimas 2 semanas, com a libertação de muitos gases intestinais? Assinale apenas uma resposta.

- ☐ 1 ENORMES PROBLEMAS
- ☐ 2 GRANDES PROBLEMAS
- ☐ 3 BASTANTES PROBLEMAS
- ☐ 4 ALGUNS PROBLEMAS
- ☐ 5 POUCOS PROBLEMAS
- ☐ 6 QUASE NENHUNS PROBLEMAS
- ☐ 7 SEM PROBLEMAS

7. De um modo geral, quais os problemas que teve, durante as últimas 2 semanas, para manter ou alcançar o peso desejado? Assinale apenas uma resposta.

- ☐ 1 ENORMES PROBLEMAS
- ☐ 2 GRANDES PROBLEMAS
- ☐ 3 BASTANTES PROBLEMAS
- ☐ 4 ALGUNS PROBLEMAS
- ☐ 5 POUCOS PROBLEMAS
- ☐ 6 QUASE NENHUNS PROBLEMAS
- ☐ 7 SEM PROBLEMAS

8. Quantas vezes, durante as últimas 2 semanas, se sentiu descontraído e livre de tensão? Assinale apenas uma resposta.

- ☐ 1 NUNCA
- ☐ 2 RARAMENTE
- ☐ 3 ALGUMAS VEZES
- ☐ 4 UMA BOA PARTE DO TEMPO
- ☐ 5 A MAIOR PARTE DO TEMPO
- ☐ 6 QUASE SEMPRE
- ☐ 7 SEMPRE

9. Durante quanto tempo, nas últimas 2 semanas, sentiu a necessidade de ter de se deslocar à casa de banho apesar de ter os intestinos vazios? Assinale apenas uma resposta.

- ☐ 1 SEMPRE
- ☐ 2 QUASE SEMPRE
- ☐ 3 UMA BOA PARTE DO TEMPO
- ☐ 4 ALGUMAS VEZES
- ☐ 5 POUCAS VEZES
- ☐ 6 RARAMENTE
- ☐ 7 NUNCA

10. Durante quanto tempo, nas últimas 2 semanas, se sentiu irritado em consequência do seu problema intestinal? Assinale apenas uma resposta.

- ☐ 1 SEMPRE
- ☐ 2 QUASE SEMPRE
- ☐ 3 UMA BOA PARTE DO TEMPO
- ☐ 4 ALGUMAS VEZES
- ☐ 5 POUCAS VEZES
- ☐ 6 RARAMENTE
- ☐ 7 NUNCA

 Portuguese (Portugal)

5. WPAI

Questionário sobre a Produtividade no Trabalho e Incapacidade de Realizar Actividades: Fístulas Perianais Complexas, V2.0 (WPAI:Fístulas Perianais Complexas)

As perguntas seguintes referem-se ao efeito da(s) sua(s) fístula(s) perianal(ais) na sua capacidade de trabalhar e de realizar atividades normais. *Preencha os espaços em branco ou assinale com um círculo um número, conforme indicado.*

1. Está empregado no momento (recebe salário)? _____NÃO ____SIM
   Se NÃO, assinale "NÃO" e passe para a pergunta 6.

As próximas perguntas referem-se aos **últimos sete dias**, sem incluir o dia de hoje.

2. Durante os últimos sete dias, quantas horas de trabalho perdeu devido aos problemas associados com a(s) sua(s) fístula(s) perianal(ais)? *Inclua as horas perdidas com dias não trabalhados por estar doente, as vezes em que chegou mais tarde ao trabalho, que saiu mais cedo, etc., por causa da(s) fístula(s) perianal(ais). Não inclua as vezes que faltou ao trabalho para participar neste estudo.*

   _____HORAS

3. Durante os últimos sete dias, quantas horas de trabalho perdeu por qualquer outro motivo, como férias, feriados ou para participar neste estudo?

   _____HORAS

4. Durante os últimos sete dias, quantas horas trabalhou efetivamente?

   _____HORAS *(Se "0", passe para a pergunta 6.)*

5. Durante os últimos sete dias, até que ponto a(s) sua(s) fístula(s) perianal(ais) afetou(aram) a sua produtividade enquanto estava a trabalhar?

Considere os dias em que ficou limitado em relação à quantidade ou ao tipo de trabalho que pôde realizar, os dias em que realizou muito menos do que gostaria ou os dias em que não conseguiu trabalhar de forma tão cuidadosa como o normal. Se a(s) fístula(s) perianal(ais) apenas afetou(aram) um pouco o seu trabalho, escolha um número baixo. Escolha um número alto se a(s) fístula(s) perianal(ais) afetou(aram) muito o seu trabalho.

Considere apenas até que ponto a(s) fístula(s) perianal(ais) afetou(aram) a sua produtividade enquanto estava a trabalhar.

A(s) fístula(s) perianal(ais) não teve(tiveram) nenhum efeito sobre o meu trabalho	0 1 2 3 4 5 6 7 8 9 10	A(s) fístulas(s) perianal(ais) impediu-me(impediram-me) completamente de realizar o meu trabalho

COLOQUE UM CÍRCULO EM TORNO DE UM NÚMERO

6. Durante os últimos sete dias, até que ponto a(s) fístula(s) perianal(ais) afetou(aram) a sua capacidade de realizar as suas atividades diárias normais não relacionadas com o trabalho?

Atividades normais significam aquilo que faz habitualmente, como tarefas domésticas, fazer compras, cuidar das crianças, fazer exercício, estudar, etc. Considere as vezes em que ficou limitado em relação à quantidade ou ao tipo de atividades que pôde realizar e as vezes em que fez menos do que gostaria. Se a(s) fístula(s) perianal(ais) apenas afetou(aram) um pouco as suas atividades normais, escolha um número baixo. Escolha um número alto se a(s) fístula(s) perianal(ais) afetou(aram) muito as suas atividades.

Considere apenas até que ponto a(s) fístula(s) perianal(ais) afetou(aram) a sua capacidade de realizar as suas atividades diárias normais, não relacionadas com o trabalho.

A(s) fístula(s) perianal(ais) não teve(tiveram) nenhum efeito sobre as minhas atividades diárias	0 1 2 3 4 5 6 7 8 9 10	A(s) fístula(s) perianal(ais) impediu-me (impediram-me) completamente de realizar as minhas atividades diárias

COLOQUE UM CÍRCULO EM TORNO DE UM NÚMERO

6. Wexner score

Escala de classificação de continência

Tipo de	**Frequência**				
incontinência	Nunca	Raramente	Algumas vezes	Frequentemente	Sempre
Sólida	0	1	2	3	4
Liquida	0	1	2	3	4
Gás	0	1	2	3	4
Uso de penso	0	1	2	3	4
Alteração do estilo de vida	0	1	2	3	4

0-perfeito
20-incontinência total

Nunca=0
Raramente=<1/mês
Algumas vezes=<1/semana,≥1/mês
Frequentemente=<1/dia,≥1/semana
Sempre=≥1/dia

7. PDAI

Índice de Atividade da Doença de Crohn Perianal (Perianal Crohn's Disease Activity Index, PDAI)

Instruções para Índice de Atividade de Doença de Crohn Perianal (PDAI)

A PDAI é uma escala que avalia a gravidade atual da doença de Crohn que envolve a área perianal.

Os itens 1 a 3 são colocados diretamente ao doente. É pedido ao doente que "Por favor considere os seus sintomas perianais e não o estado de saúde geral ou outros sintomas relacionados com a doença de Crohn para o seguinte":

Ao fazer a pergunta relativa à descarga perianal

Para o item n.º 1

Teve qualquer descarga da área perianal na última semana devido à qual tenha sujado a roupa interior ou por causa da qual tivesse de utilizar um penso para absorver? Podem ser-lhes apresentadas ou lidas as cinco opções de resposta.

1. Atividade de doença perianal

Descarga

0 Sem descarga
1 Descarga mínima de muco
2 Descarga moderada de muco ou purulenta
3 Descarga substancial
4 Mancha fecal muito evidente

Para o item n.º 2, ao perguntar sobre a dor, deve relacionar-se especificamente com a dor perianal.

Teve qualquer dor perianal e/ou restrição das suas atividades devido à dor à volta da zona perianal na última semana? Podem ser apresentadas ou lidas ao participante as cinco opções de resposta.

2. Dor/restrição de atividades

0 Sem dor/sem restrição de atividades
1 Desconforto ligeiro, sem restrição
2 Desconforto moderado, com alguma limitação de atividade
3 Desconforto acentuado, limitação acentuada
4 Dor grave, limitação grave

Para o item n.º 3, deverá relacionar-se especificamente com a doença de Crohn perianal

Teve alguma restrição na sua atividade sexual devido à sua doença de Crohn perianal na última semana? Podem ser apresentadas ou lidas ao participante as cinco opções de resposta.

3. Restrição da atividade sexual

0 Sem restrição da atividade sexual
1 Restrição ligeira da atividade sexual
2 Limitação moderada da atividade sexual
3 Limitação acentuada da atividade sexual
4 Incapaz de se envolver em atividade sexual

Os itens 4 e 5 devem ser preenchidos pelo médico prestador de cuidados de saúde após exame da área perianal.

4. Tipo de doença perianal

0 Sem doença perianal/pólipos cutâneos
1 Fissura anal ou laceração da mucosa
2 <3 fístulas perianais
3 ≥3 fístulas perianais
4 Ulceração ou fístulas do esfíncter anal com enfraquecimento significativo da pele

5. Grau de endurecimento

0 Sem endurecimento
1 Endurecimento ligeiro
2 Endurecimento moderado
3 Endurecimento substancial
4 Flutuação/abcesso muito evidente

Pontuação total: _____(soma das respostas 0-20)

A pontuação PDAI é a soma das respostas para todos os 5 itens (intervalo 0-20); uma pontuação mais alta indica doença e restrição mais grave. Os dados sobre a validação do índice podem ser consultados no artigo abaixo:

E. J. Irvine McMaster IBD Study Group. Usual therapy improves perianal Crohn's disease as measured by a new disease activity index. J Clin Gastroenterol. 1995 Jan;20(1):27-32 PMID: 7884173