Study Information

Title	Observational, real-world study of INFLECTRA in patients with inflammatory bowel disease (IBD) in the United States and Canada
Protocol number	C1231006
Protocol version identifier	3.0
Date of last version of protocol	26 January 2018
EU Post Authorisation Study (PAS) register number	EUPAS22444
Medicinal product	CT-P13 (INFLECTRA®/infliximab-dyyb)
Research question and objectives	Primary Objective 1. To describe drug use patterns, treatment adherence and associated costs in adult UC and CD cohorts treated with INFLECTRA in a real-world setting. Secondary Objectives 2. To assess real-world clinical and economic outcomes related to disease severity in adult UC and CD cohorts who initiated therapy with INFLECTRA as their first biologic, switched to INFLECTRA from REMICADE or, switched to INFLECTRA from another biologic. 3. To assess real-world patient reported quality of life in both the UC and CD cohorts who initiated therapy with INFLECTRA as their first biologic, switched to INFLECTRA from REMICADE or, switched to INFLECTRA from another biologic. 4. To describe the demographic and clinical characteristics of patients receiving INFLECTRA for the treatment of UC and CD. 5. To assess healthcare resource utilization and indirect costs in adult patients receiving INFLECTRA for the treatment of UC or CD patients receiving INFLECTRA for Ulcerative Colitis or Crohn's

	Disease. CCI [redacted]
Authors	**Pfizer, Inc** PPD [redacted] **Pharmerit International:** PPD [redacted] PPD [redacted]

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1. LIST OF ABBREVIATIONS

Table 1. List of Abbreviations

AE	Adverse event
AEM	Adverse event monitoring
ANOVA	Analysis of variance
CCI	[redacted]
CD	Crohn's disease
CDAI	Crohn's disease activity index
CRF	case report form
CRP	C-reactive Protein
ED	Emergency department
EMEA	European Medicines Agency
ESR	Erythrocyte sedimentation rate
FDA	Food and Drug Administration
IBD	Inflammatory bowel disease
NIS	Non-interventional study
pMAYO	partial MAYO score
SAE	Serious Adverse event
SIBDQ	short inflammatory bowel disease questionnaire
TNF-α	Tumor Necrosis Factor-alpha
TSQM	Treatment Satisfaction Questionnaire for Medication
UC	Ulcerative Colitis
VAS	Visual Analog Scale
WPAI	Work and Productivity and Activity Impairment

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
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3. ABSTRACT

Title

Observational, real-world study of INFLECTRA in patients with inflammatory bowel disease (IBD) in the United States and Canada; Version 3.0; 25 January 2018; PPD , MD. MSc. MPH, PPD , Pfizer, Inc.

Rationale and Background

In September 2013 CT-P13 (infliximab-dyyb), the first biosimilar in the class of TNF-α therapies, was approved in Europe, and marketed as REMSIMA® and INFLECTRA.® The biosimilar was approved for use based on clinical trials conducted in Rheumatoid Arthritis and Ankylosing Spondylitis. This European approval was extended to all of the other indications for which the originator product, REMICADE® (infliximab) was approved, based on the concept of extrapolation.[1] The European Medicines Agency concluded that extrapolation of clinical efficacy and safety profile data to other indications of the originator product, not specifically studied during the clinical development of the biosimilar was possible based on the overall evidence of comparability provided from the comparability exercise and included adequate justification that the products did not differ in a clinically meaningful manner. In response to concern from gastroenterologists on the lack of clinical data supporting the utilization of INFLECTRA in patients with inflammatory bowel disease (Crohn's disease [CD] and ulcerative colitis [UC]),[2] researchers in Europe and Asia initiated prospective and retrospective studies to collect real world data on the use of INFLECTRA in patients with inflammatory bowel disease (IBD).[3-9] The published results of these studies showed that there was no difference in the safety and efficacy between the originator and the biosimilar.

In April 2016, INFLECTRA, was approved by the FDA for the following indications:[10]

- adult patients and pediatric patients (ages six years and older) with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy;
- adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy;
- patients with moderately to severely active rheumatoid arthritis in combination with methotrexate;
- patients with active ankylosing spondylitis (arthritis of the spine);
- patients with active psoriatic arthritis;
- adult patients with chronic severe plaque psoriasis.

To date, there has been no real world data published on the use of INFLECTRA in the US population.

Research Questions and Objectives

The purpose of this study is to collect and analyze data in adult patients with IBD (CD and UC) treated with INFLECTRA in a real-world setting. There will be no imposed experimental intervention, and treatment with INFLECTRA is determined solely by the patient's physician separately and irrespective of the decision to participate in this study. The data captured and reported will reflect a real-world approach to the treatment of patients with IBD administered INFLECTRA.

The primary objective of this study is:

1. To describe drug utilization patterns, treatment adherence and associated costs in adult UC and CD cohorts treated with INFLECTRA in a real-world setting.

The secondary objectives of this study are:

2. To describe real-world clinical and economic outcomes in adult UC and CD cohorts who initiated therapy with INFLECTRA as their first biologic, switched to INFLECTRA from REMICADE or, switched to INFLECTRA from another biologic.

3. To describe real-world patient reported quality of life in both the UC and CD cohorts who initiated therapy with INFLECTRA as their first biologic, switched to INFLECTRA from REMICADE or, switched to INFLECTRA from another biologic.

4. To describe the demographic and clinical characteristics of patients receiving INFLECTRA for the treatment of UC and CD.

5. To describe healthcare resource utilization and indirect costs in adult patients receiving INFLECTRA for the treatment of UC or CD.

CCI [redacted]

CCI [redacted]

Study Design

This is a prospective, observational, multicenter study conducted in adult patients with UC or CD. The study plans to recruit 300 subjects in the United States and Canada in which the participating physician has decided to treat with INFLECTRA. The study will evaluate treatment patterns, adherence, disease activity, remission status, relapse status, treatment satisfaction, and healthcare resource utilization. Patient outcomes will be assessed at four time points (quarterly) for approximately 52 weeks after the decision to initiate treatment with INFLECTRA.

Population:

Inclusion and Exclusion Criteria

Patients must meet all the following criteria to be eligible for inclusion in the study:

1. Patients with confirmed diagnosis of Ulcerative Colitis or Crohn's Disease.
2. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.
3. Patient eligible to receive INFLECTRA for the treatment of their disease per approved drug label (patients with fistula, or stoma are eligible).

Patients meeting any of the following criteria will not be included in the study:

1. Patient age less than 18 years at the time of consent;
2. Patient previously failed treatment with REMICADE or INFLECTRA/CT-P13.
3. Any reported contraindications for INFLECTRA or REMICADE.
4. Known hypersensitivity (including severe, acute infusion reactions) to infliximab, its excipients or other murine proteins, at the time of enrolment.
5. Patients with communication difficulties in reading or understanding the study consent and questionnaires.

Variables

The tables below describe key study variables collected within this study. Exposure variables are limited to the dosing and timing of administration of INFLECTRA, as well as the dose and frequency of disease related concomitant medications. Outcomes variables are primarily limited to the responses from various patients reported outcomes including the Harvey-Bradshaw Index (HBI), partial MAYO score, Simplified Inflammatory Bowel Disease questionnaire (SIBDQ), the Work Productivity and Activity Index (WPAI), CCI [redacted] CCI [redacted] a Visual Analogue Scale (VAS), and the Treatment Satisfaction Questionnaire (TSQM). For use in more complex statistical modeling, key covariates will be limited to basic demographic information, as well as medical history, and treating physician characteristics.

Data Sources

The patient's medical record will serve as the primary data source. For patient reported outcomes, the disease specific questionnaires will be retained as the primary source document. All data will be extracted and transcribed into an electronic CRF by site personnel.

Study Size

This study will involve 30-40 clinical sites and recruit up to 300 patients, with a minimum of 100 patients in each cohort diagnosed with ulcerative colitis or Crohn's disease.

Data Analysis

This study will be primarily descriptive in nature. All categorical endpoints will be summarized using both the number and percentage in each category. Continuous endpoints will be summarized in the form of means, standard deviation (SD), median, interquartile ranges (IQR) and range; a 95% confidence interval (CI) for the mean will also be computed. Pearson's chi-squared tests will be used for bivariate statistical testing of categorical and ordinal outcomes. Student's t-tests or 1-way ANOVA will be used for comparisons of continuous outcomes. For highly skewed, non-normally distributed endpoints or sample sizes under 30 in either group, non-parametric Wilcoxon rank-sum test will be applied. All inferences will be made assuming a two-sided test with an alpha of 0.05 without adjustment for multiplicity. Approaches to controlling for baseline differences between groups such as inverse probability weights may be considered.

Milestones

Milestone	**Planned date**
Start of data collection	01 Feb 2018
End of data collection	30 Jun 2019
Registration in the EU PAS register	29 Jan 2018
Final study report	09 Sep 2019

4. AMENDMENTS AND UPDATES

Amendment number	Date	Substantial or administrative amendment	Protocol section(s) changed	Summary of amendment(s)	Reason
1	18-Oct-2017	Administrative	Several	Minor textual changes plus addition of outcome measure.	KOL/Study team review
2	25-Jan-2018	Substantial	Several	Voluntary PASS designation. Additional textual clarification.	ENAC and EUQPPV Review
3	09- Sep-2020	Administrative	Several	Additional text for sample size and recruitment	Changes in description of sample size and recruitment strategy

5. MILESTONES

Milestone	Planned date
Start of data collection	01 Feb 2018
End of data collection	30 Jun 2019
Registration in the EU PAS register	29 Jan 2018
Final study report	09 Sep 2019

6. RATIONALE AND BACKGROUND

REMICADE® (infliximab) is monoclonal antibody in a class of drugs referred to as anti-tumor necrosis factor alpha (TNF-α). It was initially approved in the United States in August 1998 for the treatment of Crohn's disease (CD),[11] in November 1999 for the treatment of rheumatoid arthritis (RA),[12] and September 2005 for the treatment of ulcerative colitis (UC).[13] In 2011, Remicade was approved for use in pediatric forms of Crohn's disease and ulcerative colitis. It is also approved for treatment of ankylosing spondylitis, psoriatic arthritis, and plaque psoriasis.[13]

In September 2013 CT-P13 (infliximab-dyyb), the first biosimilar in the class of TNF-α therapies, was approved in Europe, and marketed as REMSIMA® and INFLECTRA.® The biosimilar was approved for use based on clinical trials conducted in Rheumatoid Arthritis and Ankylosing Spondylitis. This approval was extended to all of the other indications for which the originator product, REMICADE® (infliximab) was approved, based on the concept of extrapolation[1] The European Medicines Agency concluded that extrapolation of clinical efficacy and safety profile data to other indications of the originator product, not specifically studied during the clinical development of the biosimilar was possible based on the overall evidence of comparability provided from the comparability exercise and included adequate justification that the products did not differ in a clinically meaningful manner.. In response to concern from gastroenterologists on the lack of clinical data supporting the utilization of INFLECTRA in patients with inflammatory bowel disease (Crohn's disease [CD] and ulcerative colitis [UC]),[2] researchers in Europe and Asia initiated prospective and retrospective studies to collect real world data on the use of INFLECTRA in patients with inflammatory bowel disease (IBD).[3-9] The published results of these studies reported no significant difference in the safety and efficacy between the originator and the biosimilar.

In Hungary, Gecse et al[4] conducted a prospective, nationwide, multicenter observational cohort study of 210 consecutively enrolled patients with IBD (n=126 UC, n=84 UC) initiating treatment with INFLECTRA. At week 14, 81.4% of CD and 77.6% of UC patients showed a clinical response and 53.6% of CD and 58.6% of UC patients were in clinical remission. Clinical remission rates at week 14 were significantly higher in CD and UC patients who were infliximab naïve, compared with those with previous exposure to the Remicade [$p < 0.05$]. Adverse events were reported in 17.1% of all patients through week 30. Infusion reactions and infectious adverse events occurred in 6.7% and 5.7% of all patients, respectively.

In the Netherlands, Smits et al[8] conducted a prospective observational cohort study of 83 patients with IBD (57 CD, 24 UC, 2 IBD-Undefined). The median change in disease activity (Harvey-Bradshaw Index) was 0 for CD and 0 for UC/IBD-U. Median CRP and FCP levels did not change significantly during follow-up. The median infliximab trough level increased from 3.5 μg/ml [range 0–18] to 4.2 μg/ml [range 0–21] at week 16 [p = 0.010]. Two patients developed a new detectable anti-drug antibody (ADA) response during follow-up and 5 patients discontinued INFLECTRA. No serious adverse events occurred.

In Norway, Jorgensen et al.[14] conducted randomized, non-inferiority, double-blind phase 4 trial with 52 weeks of follow up (NOR-SWITCH). Patients who enrolled in the study were randomized to remain on infliximab or switch CT-P13. A total of 482 patients enrolled (241 to infliximab, 241 to CT-P13). Patients had a mix of autoimmune diseases (32% Crohn's disease, 19% ulcerative colitis, 16% ankylosing spondylitis, 16% rheumatoid arthritis, 7% chronic plaque psoriasis 6% psoriatic arthritis). Disease worsening occurred in 26% of the infliximab group, and 30% in the CT-P13 group (per-protocol set; adjusted treatment difference −4·4%, 95% CI −12·7 to 3·9). The frequency of adverse events was similar between groups (for serious adverse events, 24 (10%) for infliximab originator vs 21 [9%] for CT-P13. The NOR-SWITCH trial showed that switching from infliximab to CT-P13 was not inferior to continued treatment with infliximab.

In April 2016, INFLECTRA, was approved by the FDA for the following indications:[10]

- adult patients and pediatric patients (ages six years and older) with moderately to severely active Crohn's disease who have had an inadequate response to conventional therapy;
- adult patients with moderately to severely active ulcerative colitis who have had an inadequate response to conventional therapy;
- patients with moderately to severely active rheumatoid arthritis in combination with methotrexate;
- patients with active ankylosing spondylitis (arthritis of the spine);
- patients with active psoriatic arthritis;
- adult patients with chronic severe plaque psoriasis.

To date, there has been no real world data published on the use of INFLECTRA in the US population.

This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is conducted voluntarily by Pfizer.

7. RESEARCH QUESTION AND OBJECTIVES

The purpose of this study is to collect and analyze data on patients with IBD treated with INFLECTRA in a real-world setting. There will be no imposed experimental intervention and treatment with INFLECTRA is determined solely by the patient's physician prior to study enrollment. The data captured and reported will reflect a real-world approach to the treatment of patients with IBD administered INFLECTRA.

7.1. Primary Objective

1. To describe drug use patterns, treatment adherence and associated costs in adult UC and CD cohorts treated with INFLECTRA in a real-world setting.

7.2. Secondary Objectives

The secondary objectives of this study are:

2. To assess real-world clinical and economic outcomes related to disease severity in adult UC and CD cohorts who initiated therapy with INFLECTRA as their first biologic, switched to INFLECTRA from REMICADE or, switched to INFLECTRA from another biologic.

3. To assess real-world patient reported quality of life in both the UC and CD cohorts who initiated therapy with INFLECTRA as their first biologic, switched to INFLECTRA from REMICADE or, switched to INFLECTRA from another biologic.

4. To describe the demographic and clinical characteristics of patients receiving INFLECTRA for the treatment of UC and CD.

5. To assess healthcare resource utilization and indirect costs in adult patients receiving INFLECTRA for the treatment of UC and CD.

CCI [redacted]

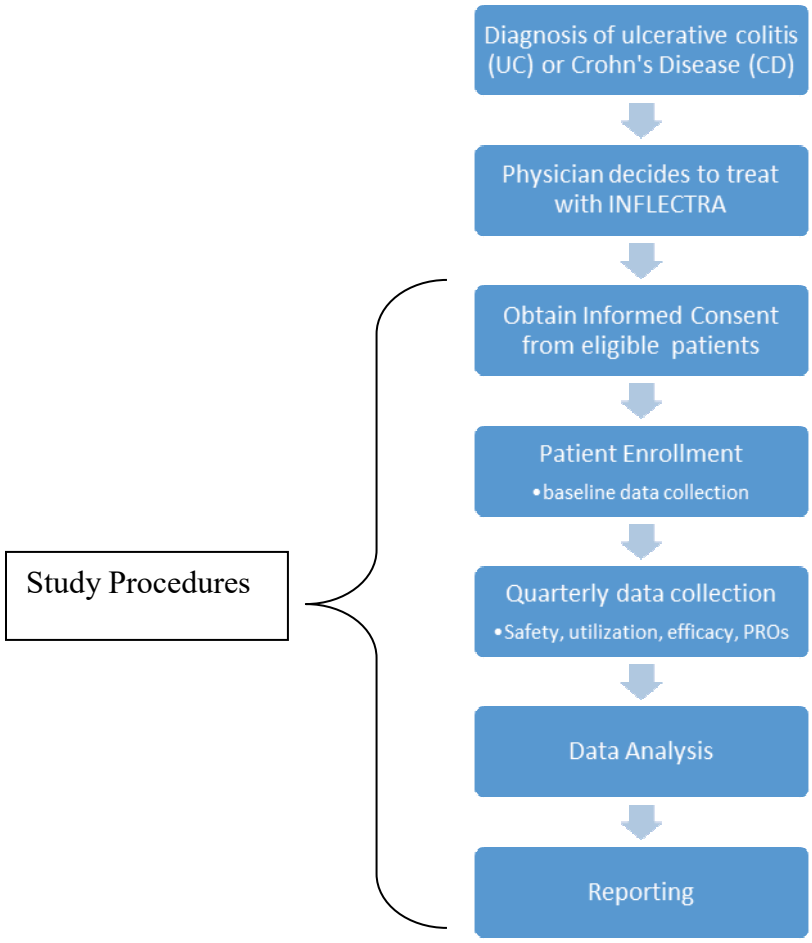
CCI [redacted]

8. RESEARCH METHODS

8.1. Study Design

This is a prospective, observational, multicenter study conducted in patients with UC and CD. The study plans to recruit 300 subjects in the United States and Canada initiating or switching to treatment with INFLECTRA over an 8 month period. The decision to start INFLECTRA will be entirely a clinical decision made by the participating physician irrespective of this study. The study will evaluate direct medical costs, indirect costs, disease activity, remission status, relapse status, treatment patterns, treatment satisfaction, and healthcare resource utilization. There are no mandated study visits, as patients will follow local standard of care. Patients will be assessed at regular intervals that coincide with regularly scheduled appointments, for 52 weeks after initiating treatment with INFLECTRA.

Figure 1. Study Design



Clinical information will be recorded in the patients chart during each treatment/clinical visit. Data entry into the EDC system will occur quarterly, along with the administration of PROs. Patients who discontinue treatment before the end of the study will be followed for the full duration of the study. Data collected on patients with CD and UC may be analyzed separately.

8.2. Setting

8.2.1. Site Selection and Physician Inclusion and Exclusion Criteria

A geographically dispersed sample of physicians will be screened based on pre-defined eligibility criteria and recruited from a list of physicians for each specialty. These physicians will then be asked to complete a self-administered survey questionnaire to describe the types of patients within their practice (eg, total caseload, estimated number of patients with each disease, estimated number of patients diagnosed by year). These physicians (and/or their assigned staff) will also be responsible for abstracting clinical data from patient records, collecting patient completed questionnaires, and data entry into the case report form. Physician inclusion and exclusion criteria are described below:

Physician Inclusion Criteria

- Certified to practice in the United States or Canada;
- Must agree to study rules including resolution of data queries including missing data;
- Routinely uses standard lab testing to monitor patient health;
- Access to certified laboratory for basic lab testing;
- Available medical records and proper documentation for patients.

Physician Exclusion Criteria

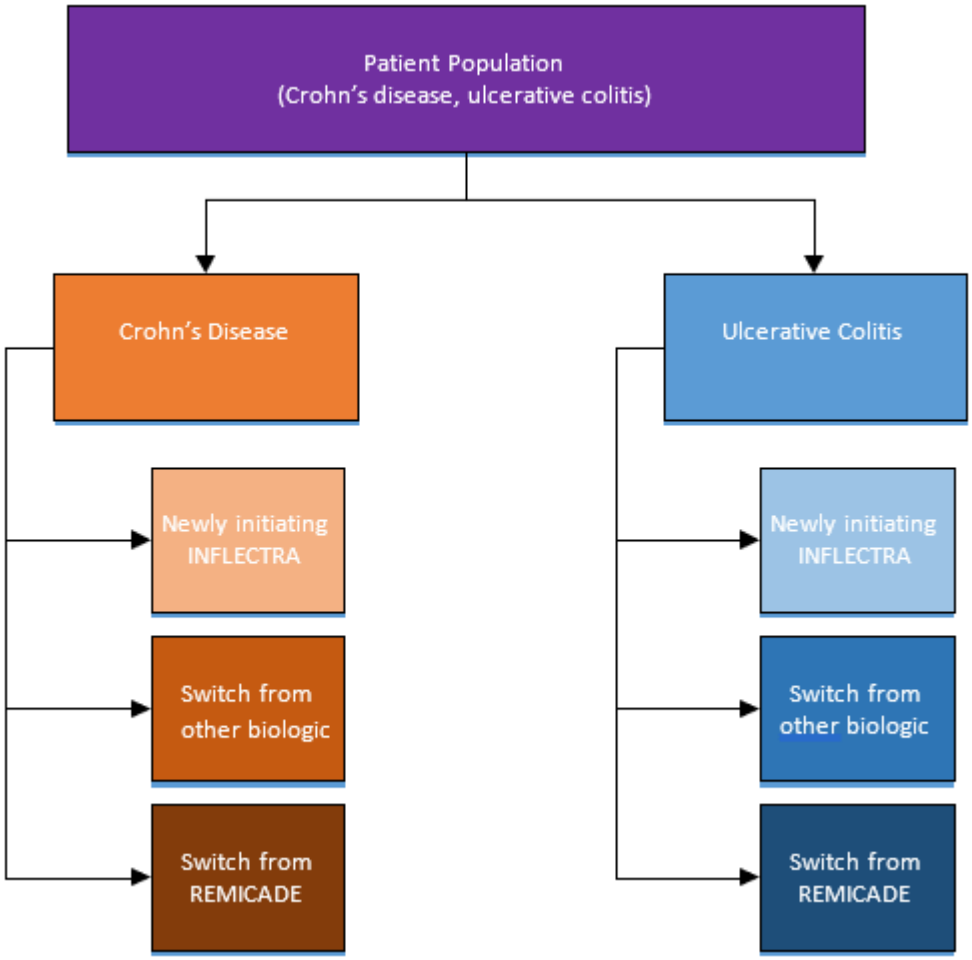
- Unwilling or unable to follow study procedures;
- Unwilling to prescribe biosimilars;

8.2.2. Study Population

This is an observational study; therefore the decision to treat a patient with INFLECTRA must be made prior to a decision to enroll them in this study. Patients are eligible to participate if they have:

- Initiated therapy with INFLECTRA as their first biologic;
- Switched to INFLECTRA while in remission on a stable dose of REMICADE; or,
- Switched to INFLECTRA from another biologic, due to non-responsiveness, intolerance, or other reasons.

Figure 2. Distribution of Eligible Patients



8.2.3. Inclusion Criteria

Patients must meet all of the following criteria to be eligible for inclusion in the study:

1. Patients with confirmed diagnosis of Ulcerative Colitis or Crohn's Disease.

2. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

3. Patient eligible to receive INFLECTRA for the treatment of their disease per approved drug label (patients with fistula, or stoma are eligible).

8.2.4. Exclusion Criteria

Patients meeting any of the following criteria will not be included in the study:

1. Patient age less than 18 years at the time of consent.
2. Patient previously failed treatment with REMICADE or INFLECTRA/CT-P13.
3. Any reported contraindications for INFLECTRA/CT-P13 or REMICADE.
4. Known hypersensitivity (including severe, acute infusion reactions) to infliximab, its excipients or other murine proteins, at the time of enrolment.
5. Patients with communication difficulties in reading or understanding the study consent or questionnaires

8.2.5. Study Procedures

In this study, recruited physicians and/or their assigned staff will be responsible for patient identification, qualification and selection, patient interview, exam recording, data abstraction and completion of the patient case report form (CRF), which is described in greater detail below.

During the baseline visit, the following procedures will be carried out:

- Verification of eligibility criteria;
- Record demographic data, medical history, and prior disease specific concomitant medications (minimum of 12 months, unless newly diagnosed);
- Record consumption of cigarettes/nicotine products;
- Administration of baseline questionnaires;
- Completion of clinical assessments;
- Document adverse events (AE) and serious adverse events (SAEs), if applicable;
- Patient summary and disposition.

If any abnormalities are detected during the assessments, the medical practitioner will communicate the results to the patient. The medical practitioner will manage and treat the detected abnormality as per routine clinical practice. Sponsor will not fund any additional diagnostic procedures or treatment related to the detected abnormalities.

There are no protocol required medical procedures for this study. Lab tests are not required, but if recent test results are available, they should be provided in the CRF. While there are no required study visits, there are multiple patient reported questionnaires, depending on indication that should be completed at various time points (approximately) during the study (Table 2).

Table 2. Planned Schedule of Events

Procedure	Visit 1 (Baseline)	Visit 2	Visit 3	Visit 4	Unscheduled visit
	Day 0	Day 90 (±30 days)	Day 180 (±30 days)	Day 365 (±30 days)	N/A
Informed Consent	X				
Patient baseline characteristics	X				
Disease History	X				
Safety Information	X	X	X	X	X
Disease-related Resource Use	X	X	X	X	
Clinical Outcomes	X	X	X	X	
Treatment Details	X	X	X	X	
Physician Information	X				

Note: Patients typically receive infusions every 8 weeks, hence this study provides a 60 day window assuming the visit might occur within this window. All visits will be as per the participating physicians clinical care routine, and no visits are mandated by this study.

8.3. Variables

The following tables describe key study variables collected within this study.

8.3.1. Baseline Characteristics/Disease Variables

Table 3. Patient Baseline Characteristics

Variable	Cohort	Operational Definition
Age	UC, CD	Patient age at baseline
Sex	UC, CD	Female/Male
Race/ethnicity	UC, CD	Hispanic or Latino/Not Hispanic or Latino; American Indian or Alaska Native; Asian; Black or African American; Native Hawaiian or Other Pacific Islander; White; Other
Height	UC, CD	Height in meters/Height in inches
Weight	UC, CD	Weight in Kilograms/Weight in Pounds
Body Mass Index	UC, CD	(Weight in Kilograms/[Height in Meters x Height in Meters]) OR (Weight in Pounds/[Height in inches x Height in inches]) x 703

Table 3. Patient Baseline Characteristics

Variable	Cohort	Operational Definition
CCI [redacted]	CCI [redacted]	CCI [redacted]
Healthcare insurance coverage	UC, CD	Plan coverage type (PPO, POS, HMO, Medicare/Medicaid, etc.)
Smoking Status	UC, CD	Smoking history, as well as current tobacco use
Concomitant medications	UC, CD	All current medications (prescription only)

Abbreviations: CCI [redacted] UC, Ulcerative Colitis; CD, Crohn's Disease.

Table 4. Clinical and Disease Characteristics

Variable	Cohort	Operational Definition
Diagnosis	UC, CD	Ulcerative Colitis, Crohn's Disease
Diagnosis Year	UC, CD	Year of Diagnosis
Age at Onset	UC, CD	Diagnosis Year-Birth year
Disease Activity	UC, CD	Harvey-Bradshaw Index (CD only), partial Mayo score (UC only)
Montreal Classification	UC, CD	Montreal Classification of disease at baseline
Previous Surgery	UC, CD	Disease related surgical procedures
Previous Surgery Date	UC, CD	Date of disease related surgical procedures
Previous Medications	UC, CD	Disease related medications
Reason for initiation	UC, CD	Reason for initiation of a biologic

Abbreviations: UC, Ulcerative Colitis; CD, Crohn's Disease.

8.3.2. Outcomes/Endpoint Variables

Table 5. Treatment-Related Adverse Events

Variable	Cohort	Operational Definition
Event Description	UC, CD	Description of the adverse event
Date Onset	UC, CD	Date the event started
Date Stop	UC, CD	Date the event resolved
Resolution	UC, CD	Fatal; Not recovered/not resolved; recovered with sequelae possible; recovered without sequelae, recovered/resolved
Severity/Grade	UC, CD	Mild; moderate; severe; life-threatening; fatal
Serious	UC, CD	Yes/No
AE treatment	UC, CD	None, medications, non-medication treatment
Action Taken	UC, CD	None; Interrupted, Discontinued, Dose reduced,

Variable	Cohort	Operational Definition
		Dose increased, Not applicable
Attribution	UC, CD	Definite; Probable; Unlikely; Unrelated

Abbreviations: UC, Ulcerative Colitis; CD, Crohn's Disease.

Table 6. Disease-Related Resource Use

Variable	Cohort	Operational Definition
Office visits	UC, CD	Date of office visit
Infusion Visits	UC, CD	Date of visit
ED Visits	UC, CD	Date of ED visits during the observation period
Hospitalizations	UC, CD	Number and duration of hospital admissions during the observation period
Endoscopy Procedures	UC, CD	Type and number of endoscopy procedures during the observation period

Abbreviations: UC, Ulcerative Colitis; CD, Crohn's Disease; ED, Emergency Department.

Table 7. Clinical Outcomes

Variable	Cohort	Operational Definition
Harvey-Bradshaw Index	CD	Calculated score based on patient completed Harvey-Bradshaw Index
partial Mayo score	UC	Calculated score based on partial Mayo tool
Short Inflammatory Bowel Disease Questionnaire	UC, CD	Calculated score based on the patient completed short Inflammatory Bowel Disease Questionnaire
Visual Analog Scale	UC, CD	Score of the patient completed VAS instrument
WPAI	UC, CD	Calculated score of the patient completed WPAI instrument
TSQ	UC, CD	Calculated score of the TSQM instrument
CCI	[redacted]	[redacted]
CCI	[redacted]	[redacted] t
Resource Utilization	UC, CD	Questionnaire logging number of physician visits, infusion visits, ED visits, and inpatient hospitalizations
C-reactive Protein	UC, CD	Physician reported lab value of most recent CRP test
Fecal Calprotectin	UC, CD	Physician reported lab value of most recent fecal calprotectin test
Therapeutic Drug Monitoring	UC, CD	Physician reported lab value of most recent therapeutic drug monitoring test

Abbreviations: VAS, visual Analog Scale; WPAI, Work Productivity and Activity Impairment; TSQM, Treatment Satisfaction Questionnaire –Medication.

8.3.3. Exposure/Independent Variables of Interest

Table 8. Treatment Details

Variable	Cohort	Operational Definition
Prescribed Drugs	UC, CD	Generic name of prescribed drug
Treatment Start Date	UC, CD	Date of first biologic dose
Infusion Start Time	UC, CD	Time infusion was started
Infusion Stop Time	UC, CD	Time infusion was stopped
Treatment End Date	UC, CD	Date of last dose, date of prescription + days' supply
Treatment Dose	UC, CD	Total mg/kg at each infusion
Treatment Dose Adjustment	UC, CD	Dosage, date, and rationale
Treatment Switch/discontinuation	UC, CD	Yes/No
Treatment Switch/discontinuation Reason	UC, CD	Defined list (Lack of response, Lack of tolerability, Chance in Insurance coverage, Patient Preference, Dosing schedule, Other-Specify)

Abbreviations: UC, Ulcerative Colitis; CD, Crohn's Disease.

8.3.4. Other Covariates/Control Variables

Table 9. Physician Information

Variable	Operational Definition
Gender	Physician gender
Age Group	Physician age group during observation window
Practice Type	Solo, group, hospital
Hospital Type	Academic, Community (general, regional, private)
Practice Location	Urban, Rural
Practice Geography	North, South, Midwest, West
Practice Size	Number of Physicians in Practice
Years in Practice	Observation Window-Physician Graduation date
Board Certification	Yes/No, Certification Description
Staff Size	Number of nurses/staff
Onsite Infusion	Yes/No
Patient Caseload	Total number of patients meeting inclusion/exclusion criteria
Patient on Therapy Caseload	Total number of patients meeting inclusion/exclusion criteria
Treatment Guidelines/Protocols	Yes/No

8.4. Data Sources

Patient interviews and data collection will be performed by site physicians and/or their assigned staff. Recruited physicians and/or their assigned staff will be responsible for patient identification, qualification and selection, patient interview, exam taking, data abstraction, and completion of the patient CRF.

Physicians and/or site staff will be instructed to assign a unique identifier for each patient enrolled in the study to facilitate follow-up on data queries and for data validation. Patient data will be de-identified and will be reported in aggregate. Patient clinical data should be abstracted from the patient's medical chart, or in the case of the patient reported outcome measures, from the assessment tools themselves, which will serve as the source document. No other source documents will be provided.

Clinical data will be collected in electronic form by the participating physician or in collaboration with the designated site personnel. Physicians will be provided with written handouts/instructions and will be periodically contacted, at least monthly until completion and submission of all the forms. Completed forms will be thoroughly reviewed and coded after entry into the database.

At least 30% of the completed forms will be randomly selected for validations against the source document on key CRF data points such as informed consent date, diagnosis, safety events, and clinical outcomes etc. by clinical research associates (CRAs). In addition, data validation will include frequency counts, arrays, and distributions, running descriptive statistics on continuous variables, and 100% computer logic checks. Any outliers and/or missing data will be directly resolved with the participating physicians.

8.5. Study Size

The primary objective for this study is descriptive in nature. As such, precision estimates (PEs) have been provided at the 95% confidence level, in lieu of power calculations.

Table 10. Sample Size for Different Precision Levels (Assuming 95% Confidence Level)

	Sample Size for Precision of:			
Percent of patients with a given risk factor	±1%	±2.5%	±5%	±10%
90%	3458	554	139	35
70%	8068	1291	323	81
50%	9604	1537	385	97

The enrollment of new patients was stopped before reaching the minimum sample size (N = 139) determined to be necessary. The primary reason for discontinuing recruitment was lack of formulary availability/insurance coverage of infliximab-dyyb during patient enrollment. Due to the lack of uptake of biosimilars/Inflectra in the US, fewer study sites than planned were able to identify and recruit patients because infliximab-dyyb was not on their formulary or patient insurance would not cover infliximab-dyyb. To resolve this issue,

the patient enrollment timeframe was extended one year beyond the planned enrollment time, and even with this extension, the study only reached 118 patients. The final analytical sample included 115 patients after excluding 1 patient due to not meeting inclusion criteria and 2 additional patients because they did not receive infliximab-dyyb due to being given RP infliximab at their infusion center/pharmacy.

8.6. Data Management

As used in this protocol, the term case report form (CRF) should be understood to refer to an electronic data record. Patient completed questionnaires will provided in paper form to the patients and the data will be transcribed into the CRF. Site staff will be required to archive all original paper questionnaires in the local site file.

A CRF is required and should be completed for each enrolled patient. The completed original CRFs are the sole property of Pfizer and should not be made available in any form to third parties, except for authorized representatives of Pfizer or appropriate regulatory authorities, without written permission from Pfizer.

The investigator has ultimate responsibility for the accuracy, authenticity, and timely collection and reporting of all clinical, safety, laboratory data entered on the CRFs and any other data collection forms. The CRFs must be signed by the investigator to attest that the data contained on the CRFs is true. Any corrections to entries made in the CRFs, source documents must be dated, initialed and explained (if necessary) and should not obscure the original entry.

In most cases, the source documents are the patient's chart. In these cases data collected on the CRFs must match the data in those charts.

In some cases, the CRF, or part of the CRF, may also serve as source documents. In these cases, a document should be available at the investigator's site as well as at Pfizer and clearly identify those data that will be recorded in the CRF, and for which the CRF will stand as the source document.

Upon completion of final analyses, a clean, de-identified database will be delivered to Pfizer in the Pfizer preferred format, typically SAS.

Data cleaning, validations, and database lock will be conducted prior to the statistical analyses.

Data validations include 30% of completed CRFs being randomly selected to have predetermined key data points validated directly with participating physicians against the source document, and 100% machine checks, reporting of the proportion of missing data at the item/individual variable level, examination of frequencies and distributions, as well as the generation of descriptive statistics.

Missing data for information documented within the medical record will be rare because of the rigorous data collection and validation procedures that will be employed. Any missing or illegible data on any CRF will result in contacting the physician directly and submitting the form for validation of the missing data against the patient's medical chart. However, certain

information may not be available in charts, in which case it will be described as unknown/ missing.

All work will be subject to quality control and documentation procedures, to make certain the report is accurate and thorough, and the analyses can be reproduced.

8.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a Statistical Analysis Plan (SAP), which will be dated, filed and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

This study will be primarily descriptive in nature. All categorical endpoints will be summarized using both the number and percentage in each category. Continuous endpoints will be summarized in the form of means, standard deviation (SD), median, interquartile ranges (IQR) and range; a 95% confidence interval (CI) for the mean will also be computed. Pearson's chi-squared tests will be used for bivariate statistical testing of categorical and ordinal outcomes. Student's t-tests or 1-way ANOVA will be used for comparisons of continuous outcomes. For highly skewed, non-normally distributed endpoints or sample sizes under 30 in either group, non-parametric Wilcoxon rank-sum test will be applied. Analyses will be made assuming a two-sided test with an alpha of 0.05 without adjustment for multiplicity. Approaches to controlling for baseline differences between groups such as inverse probability weights may be considered. Key statistical analysis will include:

- Proportion of patients adhering to treatment regimen;
- Proportion of patients who change dosing/schedule;
- Proportion of patient who discontinue treatment and rational;
- Duration of steroid free remission;
- Treatment related costs / healthcare resource use across the different groups
- Proportion of patient remaining in clinical remission at different time points;
- Reduction in steroid use will be computed.

1.1.1. Outcome Endpoints

The tables below summarize the key endpoints that will be evaluated for each objective

Table 11. Clinical Response Outcome Endpoints

Indication	Definition
Crohn's disease (remission)	Harvey-Bradshaw Index score <5[15]
Ulcerative colitis (remission)	partial Mayo score <3 points[4,16]
Crohn's disease (response)	Reduction of Harvey-Bradshaw Score of ≥3 points from[17] baseline
Ulcerative colitis (response)	Reduction of partial Mayo score of ≥3 points from baseline[4,16]

Table 12. Patient Reported Outcome Endpoints

Indication	Definition
Crohn's Disease	Change in Short Inflammatory Bowel Disease Questionnaire (SIBDQ) from baseline
Ulcerative Colitis	Change in Short Inflammatory Bowel Disease Questionnaire (SIBDQ) from baseline
All indications	Change in Quality of Life Visual Analog Scale (VAS), from baseline

Table 13. Safety Related Outcomes for Economic Assessment

Endpoint	Definition
All Infections	Count and percentage of patients with any reported infection, to be used for estimating associated costs
All Serious Infections	Count and percentage of patients with any reported infection meeting SAE criteria, to be used for estimating associated costs
Malignancy and lymphoma	Count and percentage of patients with any reported malignancies or lymphomas, to be used for estimating associated costs
Infusion-related reactions	Count and percentage of patients with reported infusion-related reactions (Acute and other), to be used for estimating associated costs
Serious Adverse Events	Count of any adverse event that means seriousness criteria, to be used for estimating associated costs

Abbreviations: SAE, Serious Adverse Events.

Table 14. Treatment Pattern Outcome Endpoints

Endpoint	Definition
Drug Dosing	Dosing per patient defined as MG/KG, at each infusion
Dose Frequency	Counting and timing of infusions by group
Use of concomitant therapy	Count and percent of patients that added, discontinued, or switched dosing of any concomitant medications such as methotrexate, mercaptopurine, azathioprine steroids, 5ASA,

Abbreviations: UC, Ulcerative Colitis; CD, Crohn's Disease.

Table 15. Patient Characteristics Endpoints

Endpoint	Definition
Sex	Distribution of male vs female
Ethnicity	Distribution of ethnic backgrounds
Age at Onset	Average age at onset
Disease duration	Average duration of disease
Disease Activity at Baseline	Baseline score for disease specific disease activity measures (HBI [CD], pMAYO [UC])
Montreal Classification (UC, CD)	Montreal classification, by level (location, extent, behavior)
Surgical History	Percentage of patients with previous disease related surgeries
Medication History	Counts and percentages for standard medications (steroids, immunomodulators, etc) that the patients have ever taken for treatment of UC/CD
Medication Baseline	Counts and percentages for standard medications (steroids, immunomodulators, etc.) that the patients are taking at day 0
Insurance coverage	Insurance plan coverage (medical and pharmacy) categorized into Medicare/Medicaid, Private plan type
CCI [redacted]	CCI [redacted]

Abbreviations: UC, Ulcerative Colitis; CD, Crohn's Disease; HBI, Harvey-Bradshaw Index.

Table 16. Patient Satisfaction and Resource Utilization Outcome Endpoints

Endpoint	Definition
WPAI	Change from baseline in WPAI score
TSQ	Average score for treatment satisfaction score at each time point
Healthcare Resource Utilization	Count of health care related visits at each time point, including hospitalizations, ED visits, office visits, infusion clinic visits

Abbreviations; WPAI, Work Productivity and Activity Index; TSQM, Treatment Satisfaction Questionnaire; ED, Emergency Department.

8.7.1. Statistical Software

Data analysis will be undertaken using SAS/STAT software, version 9.4 of the SAS® system for Windows (Cary, NC, USA).

8.8. Quality Control

As mentioned in data management, data validations include 30% of completed CRFs being randomly selected to have predetermined key data points validated directly with participating physicians against the source document, and 100% machine checks, reporting of the proportion of missing data at the item/individual variable level, examination of frequencies and distributions, as well as the generation of descriptive statistics.

Additionally, to ensure programming quality and accuracy, the following steps will be taken:

- **Methodology review:** all methodology, from sample selection to variable calculation, will be discussed and reviewed at the time of SAP drafting.
- **Variable creation:** all proposed variable definitions will be reviewed by the principal SAS programmer and a senior SAS developer.
- **Statistical review:** statistical methods will be reviewed by a Pharmerit senior statistician as well as the Pharmerit SAS statistical programmer, project manager and senior scientific leader.
- **Output review:** SAS output will be initially reviewed by the SAS programmer for logic and reasonability. Output will then be reviewed by the project manager and senior scientific leader. Additional reports will be run by the SAS programmer, as needed, to ensure validation of SAS output. Patient counts will be verified for consistency with the expected counts when defining the cohort.

8.9. Limitations of the Research Methods

Treatment patterns, and outcomes measured within this study represent only the practices of physicians who have agreed to participate in this study, and may vary from non-responding physicians, ie, those who refused study participation, or failed to complete the study requirements on time and were excluded from the study, or who were unresponsive to the screening invitation.

Though efforts are made to ensure physician/patient inclusion/exclusion criteria are based on random selection, there are, nevertheless, risks of selection bias.

By abstracting patient lab results done prior to the infusion visit it may not reflect their current lab test results accurately. Test done in different ways that are not standardized may also vary the quality of lab test.

Not all patient characteristics will be included in the data collection (eg, income and other variables which may influence physician-prescribing behavior or treatment decisions) and cannot be accounted for in the descriptive or multivariate analyses.

Information collected on the physician survey will include best estimates of patients' treatment patterns but does not equate with a complete, detailed examination and analysis of all potential at-risk or diagnosed patient records at each physician's site/practice. Although physicians seek to record all patient experiences through examination and review of the medical charts, there may be some undercounting of events that are unknown to physicians, which may have occurred outside the office and are therefore under-represented. This may also refer to AEs. It has to be expected that not all non-serious AEs will be documented in patient charts. Furthermore, information regarding hospitalizations, ER visits, or any associated healthcare resource utilization may or may not be documented within the chart. Given this, healthcare resource utilization in particular is likely to be underestimated particularly in physicians who practice in a fully outpatient setting.

Because of the nature of this observational study, all clinical outcomes could be influenced by measurement error.

8.10. Other Aspects

Not Applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Patient Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by law. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

The informed consent form must be in compliance with local regulatory requirements and legal requirements.

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the institutional review board (IRB)/independent ethics committee (IEC) and Pfizer before use.

The investigator must ensure that each study patient is fully informed about the nature and objectives of the study and possible risks associated with participation. The investigator, or a person designated by the investigator, will obtain written informed consent from each patient before any study-specific activity is performed. The investigator will retain the original of each patient's signed consent form.

9.2. Patient Withdrawal

Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral, or administrative reasons. In any circumstance, every effort should be made to document subject outcome, if possible. The investigator should inquire about the reason for withdrawal and follow-up with the subject regarding any unresolved adverse events.

If the patient withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

9.3. Institutional Review Board/Independent Ethics Committee

It is the responsibility of the investigator to have prospective approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (eg, recruitment advertisements), if applicable, from the IRB/IEC. All correspondence with the IRB/IEC should be retained in the Investigator File. Copies of IRB/IEC approvals should be forwarded to Pfizer.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), and FDA Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, management and REPORTING of adverse events/adverse reactions and All ICH/GCP guidelines.

9.5. Single Reference Safety Document

The FDA Approved product label will serve as the single reference safety document during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study. The SRSD should be used by the investigator for prescribing purposes and guidance.

This study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AE) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to any Pfizer drug that appear in the reviewed information by the investigator must be recorded on the case report form (CRF) and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these safety events with an explicit attribution to or associated with use of, respectively, a Pfizer product, the data captured in the medical record will constitute all clinical information known regarding these adverse events. No follow-up on related adverse events will be conducted.

All research staff members will complete the Pfizer requirements regarding training on the following: "*Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)"* and any relevant Your Reporting Responsibilities supplemental training. This training will be provided to all research staff members prior to study start. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

REQUIREMENTS

The table below summarizes the requirements for recording safety events on the case report form and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in the section "Definitions of safety events".

Safety event	Recorded on the case report form	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None
Scenarios involving exposure to a drug under study, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE)

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a SAE (see section "Serious Adverse Events" below)

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to a drug under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

Reporting Period

For each patient, the safety event reporting period begins at the time of the patient's informed consent if s/he is already exposed to INFLECTRA, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (eg, patient changes his/her mind about participation, failed screening criteria, the reporting period ends on the date of the decision to not enroll the patient.

If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to INFLECTRA, the SAE also must be reported to Pfizer Safety.

Causality Assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each adverse event. For AEs with a causal relationship to INFLECTRA, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that INFLECTRA caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether INFLECTRA caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that INFLECTRA did not cause the event, this should be clearly documented on the case report form and the NIS AEM Report Form.

DEFINITIONS OF SAFETY EVENTS

Adverse Events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal Test Findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

- Test result is associated with accompanying symptoms; and/or,
- Test result requires additional diagnostic testing or medical/surgical intervention; and/or,
- Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy; and/or,
- Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

Serious Adverse Events

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

- Results in death;
- Is life-threatening;
- Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute adverse events);
- Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (eg, from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

- Social admission (eg, patient has no place to sleep);
- Administrative admission (eg, for yearly exam);
- Optional admission not associated with a precipitating medical AE (eg, for elective cosmetic surgery);
- Hospitalization for observation without a medical AE;
- Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (eg, for work-up of persistent pre-treatment lab abnormality);
- Protocol-specified admission during clinical study (eg, for a procedure required by the study protocol).

Scenarios Necessitating Reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure During Pregnancy

An exposure during pregnancy (EDP) occurs if:

1. A female becomes, or is found to be, pregnant either while receiving or having been exposed to (eg, environmental) INFLECTRA, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to INFLECTRA (maternal exposure).

   An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (eg, a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

2. A male has been exposed, either due to treatment or environmental exposure to INFLECTRA prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with INFLECTRA, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to INFLECTRA in a pregnant woman (eg, a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy; in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (eg, induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (eg, ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product.

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (eg, follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure During Breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (eg, vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication Error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

- Near misses, involving or not involving a patient directly (eg, inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);
- Confusion with regard to invented name (eg, trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.
- Medication errors that do not involve a patient directly (eg, potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:
    - An identifiable reporter;
    - A suspect product;
    - The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

10.1. Single Reference Safety Document

The FDA Approved product label will serve as the single reference safety document during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study. The SRSD should be used by the investigator for prescribing purposes and guidance.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

A final report and executive summary slide deck will be provided to Pfizer upon the completion of the study; no interim reports are currently planned. In addition, congressional abstracts and manuscripts will be considered as appropriate with respect to study results and included countries.

COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

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13. LIST OF TABLES

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ANNEX 1. LIST OF STAND ALONE DOCUMENTS

14.1. Partial Mayo Questionnaire*

Stool pattern†	Patient reports a normal number of daily stools +0 1-2 more stools than normal +1 3-4 more stools than normal +2 5 or more stools than usual +3
Most severe rectal bleeding of the day‡	none +0 Blood streaks seen in the stool less than half the time +1 Blood in most stools +2 Pure blood passed +3
Physician's Global Assessment (to be completed by Physician) §	Normal +0 Mild disease +1 Moderate disease +2 Severe disease +3
*The partial Mayo score ranges from 0 to 9, with higher scores indicating more severe disease. †Each patient serves as his or her own control to establish the degree of abnormality of the stool frequency. ‡ The daily bleeding score presents the most severe bleeding of the day. § The physicians global assessment acknowledges the two other criteria, the patient's daily recollection of abdominal discomfort and general sense of wellbeing and other observations such as physical findings and the patients performance status.	

14.2. Harvey-Bradshaw Index for Patients with Crohn's Disease

Category	Choices	Score
General well-being	very well	0
	slightly below par	1
	poor	2
	very poor	3
	terrible	4
Abdominal pain	none	0
	mild	1
	moderate	2
	severe	3
Number of liquid stools per day		
Abdominal mass	none	0
	dubious	1
	definite	2
	definite and tender	3
Complications	none	0
	arthralgia	1
	uveitis	1
	erythema nodosum	1
	aphthous ulcers	1
	pyoderma gangrenosum	1
	anal fissure	1
	new fistula	1
	abscess	1

14.3. Quality of Life Assessment Using Visual Analog Scale (VAS)

Please mark your overall well-being today (with an 'X') using the following ruler from 0 to 100. 0 indicates worst health (dying) and 100 indicates perfect health.

14.4. Short Inflammatory Bowel Disease Questionnaire

This questionnaire is designed to find out how you have been feeling during the last 2 weeks. You will be asked about symptoms you have been having as a result of your inflammatory bowel disease, the way you have been feeling in general, and how your mood has been.

Please circle the number of your choice below each question.

1. How often has the feeling of fatigue or being tired and worn out been a problem for you during the past 2 weeks?

    1. All of the time.
    2. Most of the time.
    3. A good bit of the time.
    4. Some of the time.
    5. A little of the time.
    6. Hardly any of the time.
    7. None of the time.

2. How often during the last 2 weeks have you delayed or canceled a social engagement because of your bowel problem?

    8. All of the time.
    9. Most of the time.
    10. A good bit of the time.
    11. Some of the time.
    12. A little of the time.
    13. Hardly any of the time.
    14. None of the time.

3. As a result of your bowel problems, how much difficulty did you experience doing leisure or sports activities you would like to have done during the past 2 weeks?

    1. A great deal of difficulty; activities made impossible.
    2. A lot of difficulty.
    3. A fair bit of difficulty.
    4. Some difficulty.
    5. A little difficulty.
    6. Hardly any difficulty.
    7. No difficulty; the bowel problem did not limit sports or leisure activities.

4. How often during the past 2 weeks have you been troubled by pain in the abdomen?

    1. All of the time.
    2. Most of the time.
    3. A good bit of the time.
    4. Some of the time.
    5. A little of the time.
    6. Hardly any of the time.
    7. None of the time.

5. How often during the past 2 weeks have you felt depressed or discouraged?

    1. All of the time.
    2. Most of the time.
    3. A good bit of the time.
    4. Some of the time.
    5. A little of the time.
    6. Hardly any of the time.
    7. None of the time.

6. Overall, in the past 2 weeks, how much of a problem have you had with passing large amounts of gas?

    1. A major problem.
    2. A big problem.
    3. A significant problem.
    4. Some problem.
    5. A little trouble.
    6. Hardly any trouble.
    7. No trouble.

7. Overall, in the past 2 weeks, how much of a problem have you had maintaining or getting to the weight you would like to be?

    1. A major problem.
    2. A big problem.
    3. A significant problem.
    4. Some problem.
    5. A little trouble.
    6. Hardly any trouble.
    7. No trouble.

8. How often during the past 2 weeks have you felt relaxed and free of tension?

    1. All of the time.
    2. Most of the time.
    3. A good bit of the time.
    4. Some of the time.
    5. A little of the time.
    6. Hardly any of the time.
    7. None of the time.

9. How much of the time during the past 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty?

    1. All of the time.
    2. Most of the time.
    3. A good bit of the time.
    4. Some of the time.
    5. A little of the time.
    6. Hardly any of the time.
    7. None of the time.

10. How often during the past 2 weeks have you felt angry as a result of your bowel problem?

    1. All of the time.
    2. Most of the time.
    3. A good bit of the time.
    4. Some of the time.
    5. A little of the time.
    6. Hardly any of the time.
    7. None of the time.

14.5. Work Productivity and Activity Impairment Assessment

Work Productivity and Activity Impairment Questionnaire:
Specific Health Problem V2.0 (WPAI:SHP)

The following questions ask about the effect of your PROBLEM on your ability to work and perform regular activities. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? _____ NO ___ YES
   If NO, check "NO" and skip to question 6.

The next questions are about the **past seven days**, not including today.

2. During the past seven days, how many hours did you miss from work because of problems associated with your PROBLEM? Include hours you missed on sick days, times you went in late, left early, etc., because of your PROBLEM. Do not include time you missed to participate in this study.

   _____ HOURS

3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?

   _____HOURS

4. During the past seven days, how many hours did you actually work?

   _____HOURS *(If "0", skip to question 6.)*

5. During the past seven days, how much did your PROBLEM affect your productivity while you were working?

Think about days you were limited in the amount or kind of work you could do, days you accomplished less than you would like, or days you could not do your work as carefully as usual. If PROBLEM affected your work only a little, choose a low number. Choose a high number if PROBLEM affected your work a great deal.

Consider only how much PROBLEM affected productivity while you were working.

PROBLEM had no effect on my work	0	1	2	3	4	5	6	7	8	9	10	PROBLEM completely prevented me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your PROBLEM affect your ability to do your regular daily activities, other than work at a job?

By regular activities, we mean the usual activities you do, such as work around the house, shopping, childcare, exercising, studying, etc. Think about times you were limited in the amount or kind of activities you could do and times you accomplished less than you would like. If PROBLEM affected your activities only a little, choose a low number. Choose a high number if PROBLEM affected your activities a great deal.

Consider only how much PROBLEM affected your ability to do your regular daily activities, other than work at a job.

PROBLEM had no effect on my daily activities	0	1	2	3	4	5	6	7	8	9	10	PROBLEM completely prevented me from doing my daily activities

CIRCLE A NUMBER

WPAI:SHP V2.0 (US English)

14.6. Treatment Satisfaction Questionnaire

TSQM *(Version II)*

Instructions: Please take some time to think about your level of satisfaction or dissatisfaction with the medication you are taking in this clinical trial. We are interested in your evaluation of the effectiveness, side effects, and convenience of the medication *over the last two to three weeks, or since you last used it*. For each question, please place a single check mark next to the response that most closely corresponds to your own experiences.

1. How satisfied or dissatisfied are you with the ability of the medication to prevent or treat the condition?

   ☐1 Extremely Dissatisfied

   ☐2 Very Dissatisfied

   ☐3 Dissatisfied

   ☐4 Somewhat Satisfied

   ☐5 Satisfied

   ☐6 Very Satisfied

   ☐7 Extremely Satisfied

2. How satisfied or dissatisfied are you with the way the medication relieves symptoms?

   ☐1 Extremely Dissatisfied

   ☐2 Very Dissatisfied

   ☐3 Dissatisfied

   ☐4 Somewhat Satisfied

   ☐5 Satisfied

   ☐6 Very Satisfied

   ☐7 Extremely Satisfied

3. As a result of taking this medication, do you experience any side effects at all?

☐$_1$ Yes

☐$_0$ No

4. How dissatisfied are you by side effects that interfere with your physical health and ability to function (eg, strength, energy levels)?

☐$_1$ Extremely Dissatisfied

☐$_2$ Very Dissatisfied

☐$_3$ Somewhat Dissatisfied

☐$_4$ Slightly Dissatisfied

☐$_5$ Not at all Dissatisfied

☐$_{(5)}$ Not Applicable

5. How dissatisfied are you by side effects that interfere with your mental function (eg, ability to think clearly, stay awake)?

☐$_1$ Extremely Dissatisfied

☐$_2$ Very Dissatisfied

☐$_3$ Somewhat Dissatisfied

☐$_4$ Slightly Dissatisfied

☐$_5$ Not at all Dissatisfied

☐$_{(5)}$ Not Applicable

6. How dissatisfied are you by side effects that interfere with your mood or emotions (eg, anxiety/fear, sadness, irritation/anger)?

☐1 Extremely Dissatisfied

☐2 Very Dissatisfied

☐3 Somewhat Dissatisfied

☐4 Slightly Dissatisfied

☐5 Not at all Dissatisfied

☐(5) Not Applicable

7. How satisfied or dissatisfied are you with how easy the medication is to use?

☐1 Extremely Dissatisfied

☐2 Very Dissatisfied

☐3 Dissatisfied

☐4 Somewhat Satisfied

☐5 Satisfied

☐6 Very Satisfied

☐7 Extremely Satisfied

8. How satisfied or dissatisfied are you with how easy it is to plan when you will use the medication each time?

☐1 Extremely Dissatisfied

☐2 Very Dissatisfied

☐3 Dissatisfied

☐4 Somewhat Satisfied

☐5 Satisfied

☐6 Very Satisfied

☐7 Extremely Satisfied

14.7. Health Care Resource Utilization Questionnaire

INPATIENT ADMISSIONS

- Please list in the table below all inpatient admissions **since the last study visit**.
- If patient is currently hospitalized, please check the box in the "Ongoing" column.
- If patient has no previous hospitalizations since the last study visit, please check the appropriate box below.

☐ **No hospitalizations since the last study visit**

	Admission Date (dd / mmm / yyyy)	Discharge Date (dd / mmm / yyyy)	Ongoing?	Type of Admission
1.	_ _ / _ _ _ / _ _ _ _	_ _ / _ _ _ / _ _ _ _	☐	☐ Medical ☐ Surgical ☐ Other
2.	_ _ / _ _ _ / _ _ _ _	_ _ / _ _ _ / _ _ _ _	☐	☐ Medical ☐ Surgical ☐ Other
3.	_ _ / _ _ _ / _ _ _ _	_ _ / _ _ _ / _ _ _ _	☐	☐ Medical ☐ Surgical ☐ Other

EMERGENCY ROOM VISITS

- Please list how many times the patient has been to the Emergency Room **since the last study visit.**

Type of Problem	Number of Visits
Disease Specific Problems	☐☐ visits
Other medical problems	☐☐ visits

OUTPATIENT SERVICES

- Please list how many times the patient has seen one of the following health professionals **since the last study visit**.

Health Professional	Number of Visits
General practitioner / Internist	☐☐ visits
Gastroenterologist	☐☐ visits
Other (Specify: _____)	☐☐ visits

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CCI


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CCI		C C			
CCI		C C			
CCI		C C			