Title: Perianal Fistula Procedure Validation, Matched Case Control, and Patient Journey Study

NCT Number: NCT03981939

Protocol Approve Date: 14 May 2019

Certain information within this protocol has been redacted (ie, specific content is masked irreversibly from view with a black/blue bar) to protect either personally identifiable information (PPD) or company confidential information (CCI).

This may include, but is not limited to, redaction of the following:

- Named persons or organizations associated with the study.
- Proprietary information, such as scales or coding systems, which are considered confidential information under prior agreements with license holder.
- Other information as needed to protect confidentiality of Takeda or partners, personal information, or to otherwise protect the integrity of the clinical study.

Non-Interventional Study Protocol

Title: Perianal Fistula Procedure Validation, Matched Case Control, and Patient Journey Study

Short title: PAF Validation and Burden of Illness Study

Study ID: IBD-5009

Sponsor: PPD

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

Final protocol: 14 May 2019

Section 1.0 Administrative information

1.1 Contacts

A separate contact information list will be provided to each site.

Issue	Contact
Project Oversight	PPD
Clinical Protocol Input	
Project Management	

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 *[If the protocol is signed off electronically, this page should be kept (to identify why the*

PPD

5/23/2019

Date

5/23/2019

Date

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.

PPD

STUDY SUMMARY

Name of Sponsor(s): Jefferson Tea, Vice-President Medical & Scientific Affairs, Takeda Canada	**Compound/Product:** Not applicable
Title of Protocol: Perianal Fistula Procedure Reoccurrence Rate and Patient Journey Study	
Study Number: IBD-5009	**Phase:** Not applicable
Study Design: This is an observational databases study of patients who underwent surgery for perianal fistulas in Ontario.	
Study Aim: This study aims to provide a better understanding of the disease burden of perianal fistulas within Crohn's disease in Ontario.	
Study Objectives: 1. To validate the use of procedure codes to identify patients with PAFs in administrative databases 2. To compare Crohn's patients with a PAF (cases) to matched Crohn's patients without a PAF (controls) to determine the disease burden and healthcare resource utilization of Crohn's related-related PAF in Ontario 3. To describe the patient journey among Crohn's patients following their first diagnosis of perianal fistula	
Subject Population: Subjects aged >18 inclusive, with Crohn's related perianal fistulas	
Number of Subjects: All patients in the study databases who meet all of the inclusion criteria for and none of the exclusion criteria for each objective will be used in this study.	**Study Sites:** Ontario health administrative data
Dose Level(s): Not applicable	**Route of Administration:** Not applicable
Duration of Study: Overall Study Duration: Apr 2002 – Mar 2017	
Main Criteria for Inclusion: All patients who meet the validated case definition (as described in section 6.1) will be selected from the administrative databases under study.	
Main Criteria for Exclusion:	

Patients who are below the age of 18 on the date of their procedure, or those who have missing data will be excluded. Patients who are not eligible for universal Ontario Health Insurance Plan OHIP coverage through the follow up period will also be excluded e.g., due to termination of OHIP coverage, or death.
Main Criteria for Evaluation and Analyses: This study aims to identify the unmet need in the PAF patient population. The population will be described (n, %) by age, sex, and local health integration network of residence. In addition, disease burden, (as measured by direct costs, overall and by sector), as well as healthcare resource utilization (emergency department visits, hospitalizations and outpatient visits), will be evaluated.
Statistical Considerations: Objective 1: This study will be descriptive in nature. Therefore no statistical tests will be conducted. Objective 2: This study will use statistical tests, adjusting for variable follow-up periods, to compare mean costs and healthcare resource utilization between cases and controls at pre-specified time points. If the test assumptions are violated, then alternative methods will be used as appropriate. Objective 3: This study will be descriptive in nature. Therefore no statistical tests will be conducted.
Sample Size Justification: This study is a retrospective database study. All patients who meet all inclusion and none of the exclusion criteria will be included in the study.

Table of Contents

APPENDICES

1. Sample Output Tables (dated December 3, 2018, 18 pages)

List of Abbreviations and Definition of Terms

ADR:	Adverse Drug Reactions
CA:	Competent Authority
CD:	Crohn's disease
CHMP:	Committee for Medicinal Products for Human Use
CIHI:	Canadian Institute of Health Information
CRO:	Contract Research Organisation
DAD:	Discharge Abstracts Database
ED:	Emergency Department
EMA:	European Medicines Agency
GPP:	Good Pharmacoepidemiology Practices
HCRU:	Healthcare resource utilization
ICES:	Institute for Clinical Evaluative Sciences
ICH:	International Conference on Harmonisation
IEC:	Independent Ethics Committee
IRB:	Institutional Review Board
LHIN:	Local Health Integration Network
NACRS:	National Ambulatory Care Reporting System
OCCC:	Ontario Crohn's and Colitis Cohort
OHIP:	Ontario Health Insurance Plan
PAF:	Perianal Fistula
PQI:	Product Quality Issues

RIW:	Resource Intensity Weight
RPDB:	Registered Persons Database
SAP:	Statistical Analysis Plan
SSR:	Special Situation Reports
TNF-α:	Anti-tumour necrosis factor alpha
TOH	The Ottawa Hospital

Section 2.0 Introduction

Perianal fistulas (PAFs) can develop following an anorectal abscess, and can be debilitating for patients[1,2]. PAFs are common complications in patients with Crohn's disease (CD), resulting in a higher cost burden due to increased healthcare resource use (HCRU)[3].

Globally, the incidence and prevalence of CD is higher in developed countries as compared to developing countries. The annual incidence ranges from 5 per 100,000 person-years in Asia and the Middle East to 20.2 per 100,000 person-years in North America, while prevalence ranges from 67.9 per 100,000 population in Asia and Middle East to 322 per 100,000 population in Europe[4]. Canada, in particular, has one of the highest incidence and prevalence of CD worldwide[4], with an estimated 0.7% (approximately 129,000) Canadians affected with CD[5]. Considerable differences in the incidence and prevalence of CD across the Canadian provinces have been noted. The highest incidence and prevalence were reported in Nova Scotia (annual incidence of 20.2 per 100,000 person-years and prevalence of 319 per 100,000 population) and the lowest in British Columbia (annual incidence of 8.8 per 100,000 person-years and prevalence of 161 per 100,000 population)[6]. One-third of patients with CD suffer from fistulas during their disease course with low remission rate[7]. While therapies and treatments do exist, they are associated with a range of side effects which impacts quality of life.

Several surgical and medical therapies exist for the treatment of PAF. The surgical therapies range in terms of invasiveness, and can be tailored depending on the risk of reoccurrence and side-effects[1,8]. While a draining seton is generally used first, side effects include reoccurrence and fecal incontinence[8]. The reoccurrence rate following a seton can be as high as 83% in patients with CD[9]. Examples of available surgical treatment options include advancement flaps, anal fistula plugs, and fibrin sealants[1,8]. Medical therapies include anti-tumor necrosis factor alpha (TNF-α) agents, antibiotics, immunomodulators and immunosuppressive drugs[10]. In CD patients, a combined medical and surgical approach has been shown to be more effective in treating PAF than single therapy alone[11]. Despite the availability of multiple treatment options,

perianal fistulizing CD is difficult to treat, as existing therapies have limited efficacy and are associated with complications[9,10,12]. This, in turn, affects a patient's quality of life[13].

Cx601, an allogenic expanded adipose-derived mesenchymal stem cells (eASCs), is a minimally invasive treatment option under development for PAF patients. A phase 3, randomized, double-blind, placebo-controlled study of Cx601 (ADMIRE-CD) was conducted by TiGenix (now owned by Takeda) across 49 hospitals in seven European countries and Israel. This study included 212 patients with CD and treatment-refractory PAF[14,15]. Results from the study indicated that Cx601 is a safe and effective treatment option in closing external openings compared to placebo. The primary endpoint of combined remission at 24 weeks was significantly higher among patients taking Cx601 compared to placebo (51% vs. 36%; p=0.021)[15]. The effect was maintained at Week 52 when a greater proportion of patients achieved combined remission with Cx601 compared to placebo (56% vs. 39%; p=0.010)[14].

In December 2017, the European Medicines Agency (EMA) Committee for Medicinal Products for Human Use (CHMP) granted a positive opinion for Cx601[16]. Shortly after, Takeda announced the approval of Cx601 in Europe for the treatment of perianal fistulas in adult patients with Crohn's disease with an inadequate response to at least one conventional or biologic therapy[17]. This new treatment option marks the first allogeneic stem cell therapy to receive central marketing authorization approval in Europe.

The Institute for Clinical Evaluative Sciences (ICES), is an independent, non-profit corporation in Ontario, Canada that uses data collected through the administration of Ontario's system of publicly funded health care. As a "prescribed entity" in Ontario under the Personal Health Information Protection Act (PHIPA), ICES is allowed to collect and use administrative data for the purposes of monitoring and evaluating the provincial health system, a process that is renewed every three years. As a result, the ICES data repository consists of record-level, coded and linkable health data sets. It encompasses much of the publicly funded administrative health

services records for the Ontario population eligible for universal health coverage since 1986 and is flexible to integrate research-specific data, registries and surveys. Currently, this includes health service records for as many as 13 million people.. In addition to health data from the Ontario Ministry of Health and Long Term Care, it also securely links data from a variety of health surveys and registries to provide a holistic understanding of patient health outcomes across the province. This provides a unique opportunity to follow patients over time to understand the burden of illness of PAF among Crohn's patients.

The current study aims to provide a better understanding of the disease burden and unmet need of perianal fistulas within Crohn's disease in Ontario. It will accomplish this by first validating the use of procedure codes to reliably identify patients with PAF in administrative databases. It will then compare the burden of disease and healthcare resource utilization of Crohn's patients with a perianal fistula (cases), to matched control patients without a diagnosis of perianal fistula. Finally, it will capture the five-year journey of patients following their first diagnosis of perianal fistula, stratifying them by the number and order of interventions received in their follow-up period. Burden of disease as measured by direct costs incurred by patients and healthcare resource utilization by patients will be measured.

Section 3.0 Study Objective(s) and Endpoint(s)

3.1 Study Aim

This study aims to provide a better understanding of the disease burden of perianal fistulas within Crohn's disease in Ontario.

3.1.1 Study Objectives

1. To validate the use of procedure codes to identify patients with PAFs in administrative databases
2. To compare Crohn's patients with a PAF (cases) to matched patients without a PAF (controls) to determine the impact of a PAF on disease burden, as measured by direct costs and healthcare resource utilization
3. To describe the patient journey among Crohn's patients following their first diagnosis of perianal fistula

3.2 Endpoint(s)

Objective 1 is a validation study, and will measure the sensitivity, specificity, positive predictive value and negative predictive value of various diagnosis and administrative code combinations. Objective 2 will describe cases and controls by the following variables:

- Frequencies of covariates, such as sex, age group, LHIN of residence,
- Burden of disease, as measured by direct costs, and
- Healthcare resource utilization

Objective 3 will describe five different patient journeys (see pg 53, table 5, 'Pathway Group' column):

- Frequencies of covariates, such as sex, age group, LHIN of residence,
- Burden of disease, as measured by direct costs, and
- Healthcare resource utilization

Section 4.0 Study Administrative Structure

4.1 Study Sites

This study is planned to be conducted retrospectively using Ontario administrative health databases.

4.2 Sponsor Personnel

Takeda is the sponsor for the study, and will keep a record of all relevant sponsor personnel.

4.3 Contract Research Organisation (CRO)

CCI will provide project management expertise, develop the study design, and write the protocol and all deliverables. CCI will keep a record of all involved CRO personnel.

Section 5.0 Ethics

Objective 1: Research ethics approval to conduct the retrospective chart review and validation study will be granted by the Research Ethics Board at the Ottawa Hospital.

Objectives 2 and 3: This is a secondary analysis of aggregated, deidentified data. Individual consent is not required as this is a retrospective study with a large number of patients and all data made available to the investigators will be anonymized. Patient risk will not be increased by the usage of these data.

5.1 Ethical conduct of the Study

This study will be conducted in accordance with the protocol, the current version of the Declaration of Helsinki, Good Pharmacoepidemiology Practices (GPP), ISPE GPP guideline and any local regulations.

The Sponsor 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.

The sponsor is responsible for meeting the ICH requirement for yearly updates to the IECs/IRBs, if applicable.

5.2 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 and any amendments
- Ethics approval will be sought from Institutional Review Board Services, as per ICES study requirements.

The Sponsor 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.

Section 6.0 Study Design and Plan

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 subjects.
- Epidemiological methods shall be used for the analysis of collected data.

6.1 Objective 1: Validation Study

6.1.1 Study Design

This study aims to verify the potential of using procedure codes to reliably identify patients with PAF.

6.1.2 Selection of Study Population

Study subjects will be identified from The Ottawa Hospital (TOH) data warehouse. We will begin by performing a search for patients with CD based on ICD-10 coding. A chart review will be performed to confirm the diagnosis of CD and to identify patients with and without perianal fistulas. We will select approximately 300 patients with perianal CD and 300 patients with CD but without perianal fistulas. If they have a PAF at any time, they will be categorized as "PAF positive," whereas if no PAF is found, they will be categorized as "no PAF".

The reference database will be linked to administrative data from the Institute for Clinical Evaluative Sciences' Discharge Abstract Database (DAD), National Ambulatory Care Reporting

System (NACRS) and Ontario Health Insurance Plan (OHIP) datasets. ICES captures all medical claims submitted to the Ontario Health Insurance Plan (OHIP). Therefore, 100% of out-patient, in-patient, and clinic visits in Ontario are captured by ICES. The ICES data repository comprises most of the Ontario publicly funded administrative health service records since 1986.

The Ontario DAD and NACRS databases are provided to ICES by CIHI. CIHI captures data across Canada (excluding Quebec) for inpatient and same-day surgery visits through DAD,[18] as well as emergency department visits and same-day surgery through NACRS[19]. DAD and NACRS contain a range of data including hospitalizations, day surgery, emergency department visits, and outpatient clinics[20,21]. These datasets will be linked to the Registered Person's Database (RPDB), which records demographic characteristics for patients in Ontario such as age and sex. Further, the ICES Ontario Crohn's and Colitis Cohort (OCCC) will be used; a validated dataset of Ontarians who have a diagnosis of either disease.

Each ICES dataset contributes unique information towards understanding the complete picture of PAF patient care in Ontario. The databases are completely integrated and provide end-to-end patient interactions within the Ontario public healthcare system. However, they lack visibility regarding privately reimbursed medications as well as patients who change their province of residence. For this study, all data sources will be linked at the patient-level to develop longitudinal patient-level perspectives. For all patients, relevant intervention and diagnosis codes for these patients will be extracted to construct the 12 case definitions of interest (Table 1). Patients have to have a PAF diagnosis at or after their OCCC inclusion date. If they enter the OCCC after their PAF diagnosis, their Crohn's diagnosis date in this study will set to their index date. Finally, since this is administrative data that uses an inferred algorithm, it cannot be determined whether fistula are simple or complex in nature. However, ~80% of fistula are complex, and this study will be limited to patients in a validated cohort Crohn's disease patients[2].

6.1.3 Inclusion Criteria

The inclusion criteria for this study will include:

- Inclusion in TOH "reference" database AND
- Aged 18-105 inclusive at date of index AND
- Patient can be linked between TOH "reference" database to the ICES databases based on health card number (validated using sex and date of birth) AND
- Incident inclusion in the OCCC between April 1 2002 to July 1, 2013 AND
- Incident diagnosis of PAF in TOH database between April 1 2004 to July 1, 2015

6.1.4 Exclusion Criteria

The exclusion criteria will include:

- Missing demographics at index date (sex, age, LHIN, income quintile) in all databases
- Death date in the ICES data prior to TOH PAF incidence date

The total number of patients excluded using each exclusion criteria will be reported in the final deliverable in a waterfall chart (Table 2). Subjects should be included in the study only once.

6.1.5 Statistical Analysis

All patients identified from the TOH data warehouse with and without PAF will be included in the analysis. The cohort will be profiled by age, sex, neighbourhood income quintile, and LHIN of residence (Table 3). Analyses will then be performed using the concepts of diagnostic test evaluation, following methods used in previous ICES cohort validation studies[22–28]. Sensitivity tables will be created with each of the 12 case definitions to maximize sensitivity, specificity, PPV, NPV, and AUC. Finally, positive and negative likelihood ratios will be calculated (Table 4). The case definition with the highest sensitivity will be selected, and if there is a tie, the case definition with the higher PPV will be selected. Equations for each are provided below:

- Sensitivity = true positive / (true positive + false negative)
- Specificity = true negative / (true negative + false positive)
- Positive predictive value (PPV) = true positive / (true positive + false positive)
- Negative predictive value (NPV) = true negative / (true negative + false negative)
- Positive likelihood ratio = sensitivity / 1 – specificity
- Negative likelihood ratio = 1 – sensitivity / specificity

6.2 Objective 2: Matched Case Control Study

6.2.1 Study Design

The objective of this study is to compare Crohn's patients with a PAF (cases) to matched patients without a PAF (controls) to determine the impact of a PAF on disease burden and healthcare resource utilization.

6.2.2 Selection of Study Population

Databases from the Institute for Clinical Evaluative Sciences (ICES) will be used to follow patients over time. All patients who meet the case definition will be considered PAF positive. Their index date (i.e., onset of PAF) will be selected based on the first time they meet the first code in the case definition identified in Objective 1 between April 1, 2007 to March 31, 2012. Using the Ontario Crohn's and Colitis Cohort (OCCC), their date of entry into the OCCC with a Crohn's diagnosis will be ascertained. For patients who enter the OCCC after their PAF index date, their lookback time will be set to 0 days for matching purposes; the actual difference will be reported in the output tables. If the proportion of patients who enter the OCCC after their PAF index date is less than 5% of the total sample, these patients will be excluded from the study. Patients will then be followed forward until the end of the study (March 31, 2017). Controls will be assigned the same index date as their cases, and will be matched to PAF patients on the following (Figure 1):

1. Age on index (± 5 years)

2. Sex
3. Geographic region (LHIN)
4. Match on Charlson Comorbidity Index
5. Year of inclusion in the OCCC
6. Maximum of duration from the OCCC to index date, or 0 days if OCCC entry is after the index date
7. Duration of follow-up

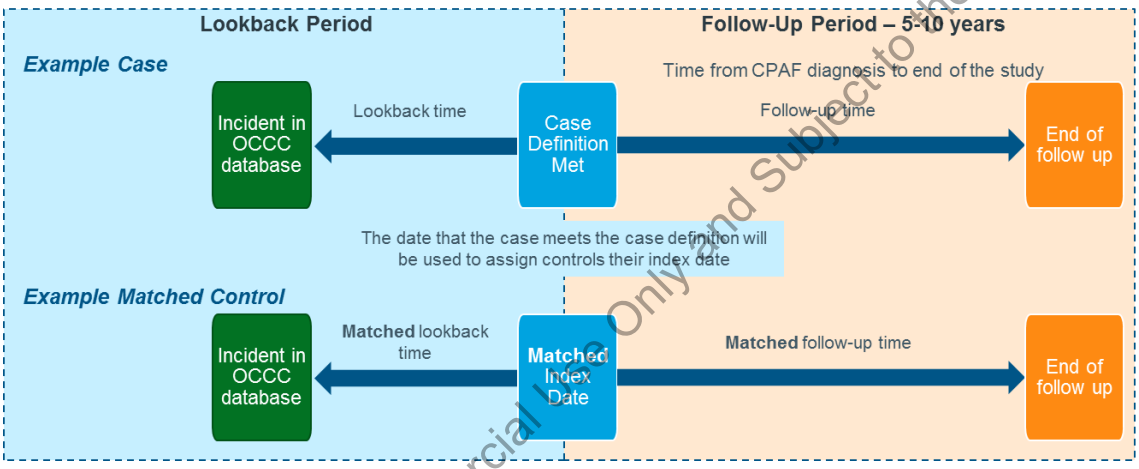

Figure 1: Case-control study design. Controls will be matched to cases on age on index, sex, geographic region (LHIN), Charlson Comorbidity Index, year of inclusion in the OCCC, duration from the OCCC to index date, and duration of follow-up

Each case will be matched to up to 4 controls. In the event that the matching criteria are too strict, the exact match for the year of inclusion in the OCCC will be modified to ±1 year. Cases for whom a matched control cannot be found will be excluded from the analysis. If this is not successful, or a large percentage of cases are excluded, propensity score matching will be used to match patients. If propensity score matching is used, duration of follow-up will not be included as a matching criterion, however, the same matching criteria as the exact matching will be used to create the propensity score match (i.e., age, sex, geographic region, CCI, and year of index).

6.2.3 Inclusion Criteria

The inclusion criteria for this study will include:

- Patients were incident in the OCCC from April 1, 2002 to March 31, 2012 AND
- The case meets the PAF case definition identified in Objective 1 in the selection period (April 1, 2005 to March 31, 2012) AND
- Aged 18-105 inclusive at date of index

6.2.4 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

- Missing demographics at index date (sex, age, neighbourhood income quintile, LHIN)
- Death during 5-year analysis period
- OHIP coverage is terminated during the follow-up e.g., if the patient moves to another province
- Meeting the case definition during the lookback period
- Cases for whom a matched control cannot be found

The total number of patients excluded using each exclusion criteria will be reported in the final deliverable in a waterfall chart (Table 5). Subjects should be included in the study only once.

6.2.5 Statistical Analysis

All eligible cases and controls will be used in this analysis. First, for cases and controls separately, their demographic characteristics on index, such as age, sex, neighbourhood income quintile, and LHIN of residence will be reported. In addition, for cases only, the average time from OCCC inclusion to case definition for PAF being met, and the calendar year in which the case definition was met will also be recorded (Table 6). If the percentage of patients who met the case definition for PAF prior to inclusion in the OCCC is above 5%, Table 6 will be duplicated, but only for patients who were already included in the OCCC when they met the case definition for PAF.

Next, the mean will be calculated for disease burden, as measured by total cost, cost by sector, and healthcare resource utilization for cases and controls. This will be done for years 0-10, 0-5 and 0-1 prior to meeting the PAF case definition, inclusive. Patients will be censored at OCCC inclusion in the lookback period. For each of these three time periods, the mean difference between cases and controls will be calculated with standard deviations, and the statistical significance of the difference evaluated (Table 7). Inverse probability weighting will be used to account for loss to follow-up in patient counts. This will then be repeated after the cases met the case definition for a PAF for years 0-1, 0-5, and 0-10, inclusive (Table 8). By design, trends over time cannot be compared as each time period may utilize different cohorts.

Finally, procedures will be categorized as EUA ± seton, advanced interventions, diversions, and proctectomy (Table 9). For each year of follow up, the total number of patients, and total number of cumulative procedures performed will be tabulated (Table 10).

6.3 Objective 3: Patient Journey Study

6.3.1 Study Design

The objective of this study is to describe the patient journey among Crohn's patients following their first diagnosis of perianal fistula

6.3.2 Selection of Study Population

As per Objective 2, databases from the Institute for Clinical Evaluative Sciences (ICES) will be used to follow patients over time. All patients incident in the OCCC from Jan 1, 2002 to March 31, 2012 will be selected. All patients who meet the case definition will be considered PAF positive. Their index date (i.e., onset of PAF) will be selected based on the first time they meet the first code in the case definition identified in Objective 1 between April 1, 2005 to March 31, 2012. Using the Ontario Crohn's and Colitis Cohort (OCCC), their date of entry into the OCCC

with a Crohn's diagnosis will be ascertained. For patients who enter the OCCC after their PAF index date, their lookback time will be set to 0 days for matching purposes; the actual difference will be reported in the output tables. If the proportion of patients who enter the OCCC after their PAF index date is less than 5% of the total sample, these patients will be excluded from the study. Patients will then be followed forward until the end of the study (March 31, 2017). Patients will then be followed forward for five years, and all relevant procedures identified in the follow-up period (Table 9).

Based on the order and number of procedures received, patients will be assigned into one of five groups (Table 11). These are:

1. No intervention: These patients receive none of the listed interventions following their first diagnosis of PAF in the five-year follow-up period
2. ≥1 EUA ± seton: Patients in this group received only EUA ± seton as part of their treatment, with no additional procedures administered
3. 2 EUA ± seton AND Advanced Intervention: These patients received 2 x EUA ± seton, followed by an advanced intervention or diversion procedure.
4. 1 EUA ± seton AND Advanced Intervention: Similar to group 2, these patients received a single EUA ± seton, followed by an advanced intervention or diversion procedure. They may have received additional procedures after this intervention.
5. Other: These patients received an advanced intervention or diversion as their 1st line treatment.

6.3.3 Inclusion Criteria

The inclusion criteria for this study will include:

- Inclusion in the OCCC at or prior to index visit with a diagnosis of Crohn's disease AND
- The case meets the PAF case definition identified in Objective 1 in the selection period AND
- Aged 18-105 inclusive at date of index AND

- Have to have 5 years of follow-up

6.3.4 Exclusion Criteria

Any subject who meets any of the following criteria will not qualify for entry into the study:

- Missing demographics at index date (sex, age, neighbourhood income quintile, LHIN)
- Death during 5-year analysis period
- OHIP coverage is terminated during the 5-year analysis period e.g., if the patient moves to another province
- Meeting the case definition during the lookback period

The total number of patients excluded using each exclusion criteria will be reported in the final deliverable in a waterfall chart (Table 11). Subjects should be included in the study only once.

6.3.5 Statistical Analysis

First, for each of the five patient pathway groups, their demographic characteristic, such as age, sex, neighbourhood income quintile, and LHIN of residence will be reported. (Table 13).

Next, the mean and standard deviation will be calculated for total burden of disease, as measured by cost, cost by sector, and healthcare resource utilization for each patient group. This will be done for the entire 5-year follow-up period (Table 14), and annualized (i.e., divided by 5) to get the average cost and HCRU per year of follow-up (Table 15).

6.4 Study Schedule

Planned Start of Study:	Apr 2002
Planned End of Study:	Dec 2017/latest data available in ICES
Planned collection of first data point:	Jan 2018

Planned collection of the last data point: Aug 2019

Planned completion of the study report: Sep 2019

6.5 Treatments

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

6.6 Premature Termination or Suspension of Study or Investigational Site

As this study is a retrospective observational database study with no investigational sites there are no requirements for premature termination or suspension of the study.

6.7 Study Plan

Description	Sep-18	Oct-18	Nov-18	Dec-18	Jan-19	Feb-19	Mar-19	Apr-19	May-19	Jun-19	Jul-19	Aug-19	Sep-19
Phase 1: Validation Study													
Protocol finalized (includes REB approval)	■												
TOH – Data extraction		■	■										
ICES – Data linkage				■	■	■	■						
IQVIA – SAP writing					■	■	■						
ICES – Analysis period								■					
Delivery to Takeda									■				
Phase 2: ICES Study													
Kick off with Takeda and KOL	■												
Protocol development	■												
KOL review		■											
Local review			■										
Global review			■	■									
Research ethics approval					■								
CCI SAP writing			■	■									
Kick off with ICES					■								
ICES data analysis						■	■	■	■	■	■	■	
Phase 3: Synthesis & summary													
Synthesize findings & conclusions											■	■	
Final report and presentation													■

Section 7.0 Safety Reporting

As this study is a retrospective observational database study with no investigational sites, and the study sponsors and CRO have no access to patient-level data there are no requirements for safety reporting in this study. No Takeda pharmaceutical products will be studied and no product-related or –unrelated adverse events will be collected. Health Canada adverse event reporting is not relevant to this study.

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 forwarded 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. This included events spontaneously notified to the investigators(s) or research team which are study endpoints and also events spontaneously notified which are not study endpoints. As such reports are spontaneously notified, causality of any adverse events should be assumed unless there is evidence to the contrary.

Section 8.0 Data Quality Control and Assurance

8.1 Quality Control

The diagnosis codes and procedures entered into the DAD and NACRS databases have been entered by an abstractor at each hospital site and have been quality checked via several mechanisms outlined in Figure 3 below[20,21].

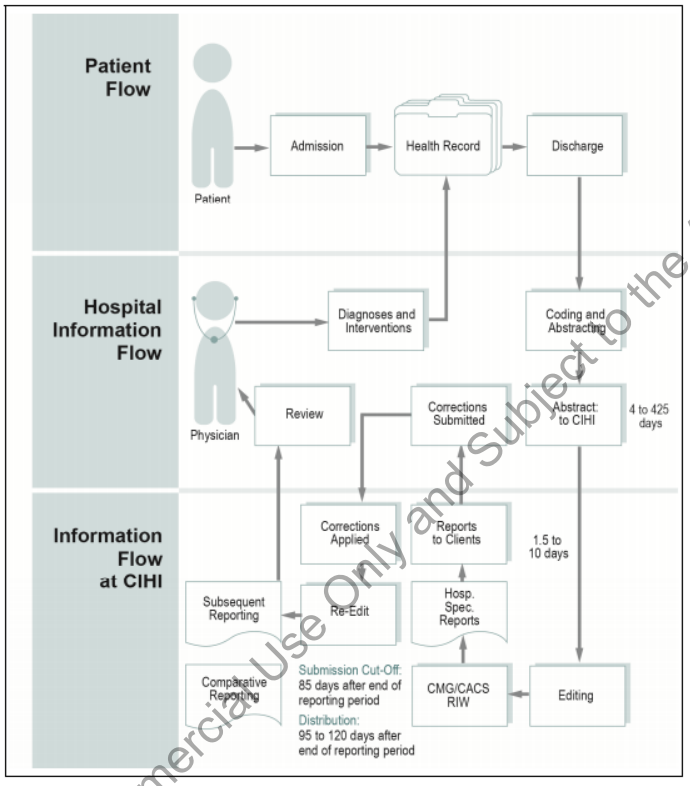

Figure 2. Discharge Abstract Database—Information Flow

8.2 Data Management

Data will be housed within secure servers at ICES, the management of which have been approved by the Office of the Information and Privacy Commissioner of Ontario under section 45 of Ontario's Personal Health Information Protection Act since 2005. Access to information is restricted by role, and is project specific. Data are analysed on these secure servers, and only the output may be extracted. The study sponsors and CRO will not have access to these data, and as such all data management and data privacy policies will be as per ICES internal protocols.

Section 9.0 Statistical Methods and Determination of Sample Size

This section describes the variables and epidemiological measurements as foreseen at the time of planning the study. Each study has an included statistical analysis section (Objective 1: Section 6.1.5, Objective 2: Section 6.2.5, Objective 3: 6.3.5). Any known deviations from the planned analyses, the reason for such deviations and all alternative / additional statistical analyses that may be performed as well as the final statistical analysis must be described in a revised Statistical Analysis Plan (SAP) before completion of data collection.

9.1 Statistical Analysis Plan

Epidemiological methods will be employed for data analyses. As noted in Section 7.0 there is no requirement to collect or report ASRs.

9.1.1 Variables and Epidemiological Measurements

9.1.1.1 Age

Patient age at index will be categorized into the following groups:

- 18-44
- 45-64, and
- ≥65

9.1.1.2 Sex

Patient sex at index will be extracted. Sex will be categorized as male or female.

9.1.1.3 Procedure and Diagnosis Codes

The following procedure and diagnosis codes will be captured in this study:

1. K60.x – Fissure and fistula of anal and rectal regions
2. 565 Fistula and Fissure
3. S251: Excision – fistula in ano (EUA + seton)
4. 3.NQ.^^.^^ Diagnostic Imaging Interventions on the Rectum

5. 3.NQ.10.^^ Xray, rectum
6. 1.NQ.86.MB for fistula terminating at skin or subcutaneous tissue [e.g. anorectal] with simple excision (with or without closure)
7. 1.NQ.86.MB-W3 using fibrin glue
8. 1.NQ.86.MB-XX-E using local transposition flap [e.g. mucosal advancement flap]
9. 1.NQ.86.MB-XX-F using free (myocutaneous) flap
10. 1.NQ.86.MB-XX-G using distant pedicled flap
11. 1.NT.86.MB open approach for fistula terminating at skin
12. 1.NT.86.MB-FA using open approach and encirclage device [e.g. seton or rubber band]
13. 1.NT.86.MB-W3 using open approach using fibrin glue
14. 1.NT.86.MB-XX-G using pedicled flap [e.g. endorectal advancement muscle flap]
15. 1.NT.86.MB-XX-L using xenograft [e.g. Surgisis anal plug]
16. 1.NM.76.^^ Colocolostomy (for exclusion and diversion)
17. 1.NM.77.^^ Colostomy (permanent, terminal, transverse loop, double barreled)
18. 1.NM.82.^^ Colostomy [any type]
19. 1.NK.77.^^ terminal, loop, end or Brooke
20. 1.NK.84.^^ Ileostomy, Continent [e.g. Kock or Barnett pouch]
    a. Note that this include 1.NK.84.^^ Proctectomy with conversion from ileostomy to continent ileostomy

9.1.1.4 Patient Local Health Integration Network (LHIN)

Patient LHIN will be extracted at index. LHIN is the geographic partition of Ontario into healthcare regions, where each region has its own set of healthcare providers and administration to coordinate care and distribute funds. There are 14 regions (Central, Central East, Central West, Champlain, Erie St. Clair, Hamilton Niagara Haldimand Brant, Mississauga Halton, North East, North Simcoe Muskoka, North West, South East, South West, Toronto Central, and Waterloo Wellington).

9.1.1.5 Index Date

The date of the first time a patient meets the case definition (Section 6.1) within the selection period will be considered the index date for cases in Objective 2, and patients in Objective 3. An index date will be assigned to controls in Objective 2 based on their matched case.

9.1.1.6 Neighbourhood Income Quintile

Neighbourhood income quintile is calculated using the postal code associated with each patient's health card number, and linking this to Census data. Within the Census data, the median income in each dissemination area (which contains 400 to 700 persons) will be calculated, and neighborhoods will be divided into income quintiles, with quintiles 1 and 5 having the lowest and highest median incomes, respectively.

9.1.1.7 Date of Diagnosis

The date of Crohn's disease diagnosis (i.e., patient entry) into the OCCC will be considered their Crohn's diagnosis date.

9.1.1.8 Lookback Period

The number of days from date of diagnosis of Crohn's disease in the OCCC to the index date.

9.1.1.9 Follow-Up Period

The number of days from the index date to the end of the study (Objective 2), or five years following the index date (Objective 3).

9.1.1.10 Cost

The cost of each visit will be calculated using the resource intensity weight (RIW) methodology from the Canadian MIS Database (CMDB), which attributes a hospital specific cost to the resource intensity of each visit[29,30].

9.2 Interim Analyses

No interim analyses are planned for this study.

9.3 Determination of Sample Size

This study is a retrospective database study, and therefore all patients who meet all of the inclusion and exclusion criteria will be included in the study.

Section 10.0 Reports

A Non-Interventional Study Report based on the results obtained will be prepared and submitted to Global Research for distribution. The Final Study Report should be available within one year from collection of the last data point, and as there are no participating sites there is no need to inform them about the results when the report is finalised.

Section 11.0 Publication, Disclosure, and Clinical Trial Registration Policy

The Sponsor aims to have the results of this study published.

The Sponsor 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.

Section 12.0 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 the Sponsor and CCI
- The study protocol and any amendments
- Signed and dated protocol agreement and amendment agreements, if any, with the original signature of the Site Responsible
- Written IEC / IRB approval / vote according to local regulations
- Authority approval according to local regulations

As this is a retrospective database study there is not requirement for storage of patient level documentation.

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