1.0 Title Page

REGISTRY STUDY PROTOCOL P06-134

A Long-Term Non-Interventional Registry to Assess Safety and Effectiveness of HUMIRA® (Adalimumab) in Subjects with Moderately to Severely Active Crohn's Disease (CD)

Incorporating Amendments 1, 2 and 3 and Administrative Changes 1, 2, 3, 4, 5, 6 and 7

AbbVie Number/ Investigational Product:	Humira® (adalimumab)
Date:	18 June 2013
Development Phase:	Post-Marketing Registry Study
Study Design:	Observational
Investigators:	Multicenter Registry (Investigator information on file at AbbVie)
Sponsor:	AbbVie Inc. (AbbVie) 1 North Waukegan Road North Chicago, IL 60064, USA
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This study will be conducted in compliance with the protocol and all other applicable regulatory requirements, including the archiving of essential documents.

1.1 Protocol Amendment: Summary of Changes

The purpose of this amendment is to:

- Section 3.1 Safety Information: Add new subsection for safety monitoring requirements.

  Rationale: To comply with an FDA requested, TNF-inhibitor class wide exploration of the rare appearance of malignancy in patients ≤ 30 years of age.

- Section 6.4.5 Prior and Concomitant Medications: Add new data collection requirements for events of malignancy in patients ≤ 30 years of age.

  Rationale: To comply with an FDA requested TNF-inhibitor class wide exploration of the rare appearance of malignancy in patients ≤ 30 years of age.

- Section 7.1.1 Adverse Events: Clarify that elective surgery/procedures performed during the registry period will not be considered SAEs if the surgery/procedure is performed for a pre-existing condition and the surgery/procedure was planned prior to enrollment in the registry.

  Rationale: To align with current AbbVie safety standards.

- Section 7.4 Adverse Event Collection Period: Clarify the duration of follow-up for patients who develop an adverse event of interest or SAE.

  Rationale: Follow-up duration is based on post-marketing reporting requirements.

- Section 7.5 Adverse Event Reporting: Add new reporting requirements for serious and nonserious events of malignancy in patients ≤ 30 years of age.

  Rationale: To comply with an FDA requested, TNF-inhibitor class wide exploration of the rare appearance of malignancy in patients ≤ 30 years of age.

- Section 7.6 Pregnancy: The data collection period for pregnancy was updated to be from the date of first dose through 150 days following the last registry dose. The requirement to register for the AbbVie sponsored pregnancy registry for US, Puerto Rico and Canada was removed. In addition, the time period to report any event of pregnancy, spontaneous abortion, stillbirth, or congenital anomaly was updated to be within 24 hours.

  Rationale: Admission to the pregnancy registry is no longer available and the reporting time for pregnancy and pregnancy related events was updated to reflect current standard SAE reporting requirements.

- Correct minor typographical and grammatical errors throughout the document.
- Administrative Changes:
  - Incorporate Administrative Change 6:
    - Title page: Update contact information and remove GCP requirement.
    - Section 6.0: Describe when an Investigator may become a Health Care Provider (HCP) in the Investigational Plan.
    - Section 6.4.5 Concomitant Medications: Add criteria regarding interventional clinical trials.
    - Section 6.5 Withdrawal of Patients from Registry: Explain how to complete the eCRF pages for discontinued or lost to follow-up patients.
    - Section 7.0 Adverse Events/Adverse Event Reporting: update the reporting period for serious adverse events and adverse events of interest to be consistent within the protocol.
    - Section 7.7 Data Collection Procedures for Patients Who Re-enroll in the Registry: Clarify event reporting procedures for patients who re-enroll into the registry.
    - Section 12.0 Completion of Registry: Clarify the definition of registry completion.

- Incorporate Administrative Change 7:
  - Change Sponsor from Abbott Laboratories (Abbott) to AbbVie in all instances found within the protocol except where outside documents are referenced and include new Sponsor address.

For an itemized list of all changes made to the protocol under this amendment, please refer to Appendix G.

2.0 Table of Contents

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3.0 Introduction

Crohn's disease (CD) encompasses a spectrum of clinical and pathological processes manifested by focal asymmetric, transmural, and occasionally, granulomatous inflammation affecting any segment of the gastrointestinal tract.[1] The prevalence of CD is approximately 140/100,000 in the United States (US) and 40 – 140/100,000 in the European Union (EU).[2] The incidence is lower in developing countries. The disease can affect persons of any age and onset is most common in the second and third decades. Males and females are affected equally. The risk for disease is higher in some ethnic groups.[3] CD is neither medically nor surgically curable thus requiring therapeutic approaches to maintain symptomatic control, improve quality of life, and minimize short and long-term toxicity and complications.[4] Despite the relatively low incidence, the cost of therapy for these subjects is estimated at two billion dollars annually in the US.[5]

No single etiologic agent has been identified as the cause for disease. There is evidence of a genetic predisposition as well as a strong association with smoking.[6] Current theories propose environmental factors in genetically predisposed hosts. The mechanism is thought to be a predisposition to an unregulated immune response to protein antigens that are present in normal intestinal microbial flora of the food stream. This can arise from a number of different immunologic defects that all result in a disease marked by excessive Type 1 T helper (Th1) T-cell response (with increased production of tumor necrosis factor-alpha [TNF-α], interleukin-2 [IL-2], and interleukin-12 [IL-12]).[7]

TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF play an important role in pathologic inflammation. There is considerable evidence for the efficacy of anti-TNF agents in CD, which includes infliximab (Remicade) use for the treatment of CD.[8,9]

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody containing only human peptide sequences. Adalimumab is produced by recombinant DNA technology in a mammalian cell expression system. It consists of 1330 amino acids and has a molecular weight of approximately 148 kilodaltons.

Adalimumab binds specifically to TNF and neutralizes the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. Adalimumab is comprised of fully human heavy and light chain variable regions, which confer specificity to human TNF, and human IgG1 heavy chain and kappa light chain sequences. Adalimumab binds with high affinity and specificity to soluble TNF-α but not lymphotoxin (TNF-β).

Adalimumab also modulates biological responses that are induced or regulated by TNF. After treatment with adalimumab, levels of acute phase reactants of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]) and serum cytokines rapidly decrease. Subjects treated with adalimumab usually experience improvement in these laboratory indicators of chronic inflammation.

As of 06 Nov 2009, adalimumab has been evaluated in approximately 24,228 subjects with rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), psoriasis (Ps) and CD, juvenile rheumatoid (idiopathic) arthritis (JRA/JIA), hidradenitis suppurativa (HS), and ulcerative colitis (UC). Adalimumab is approved for the treatment of RA, AS, PsA, CD, Ps and JIA in the EU and US.[10]

Humira® (adalimumab) was approved for the treatment of CD by the US Food and Drug Administration on 27 Feb 2007 and received the European marketing authorization approval on 04 Jun 2007. Approval was based on four controlled clinical studies that showed that adalimumab was well tolerated and the pattern and frequency of adverse events (AEs) were comparable to those seen in the other populations previously studied. Refer to the most current local product label for a summary of these studies and a comprehensive explanation of the AE profile.[11]

Fatalities, serious infections, and sepsis have been reported with the use of TNF antagonists. Many of the serious infections have occurred in subjects on concomitant immunosuppressive therapy that, in addition to their underlying immune disorder, could predispose them to infections. Tuberculosis (TB) has also been observed in subjects

treated with TNF antagonists, including adalimumab. The event rate for TB in the CD development program is consistent with the global adalimumab rate.[11]

TNF antagonists, including adalimumab, have been associated with cases of demyelinating disease. Serious allergic adverse reactions have been reported in subjects following subcutaneous administration of adalimumab.[10]

In the controlled portions of clinical trials of TNF-antagonists, more cases of malignancies including lymphoma and non-melanoma skin cancer have been observed among patients receiving a TNF-antagonist compared with control patients. However, the occurrence was rare.[12] Furthermore, there is an increased background lymphoma risk in rheumatoid arthritis patients with long-standing, highly active, inflammatory disease, which complicates the risk estimation.[13-15] Post-marketing cases of rare malignancies usually associated with immunosuppression and malignancies that are not usually observed in children and adolescents have been reported with use of TNF antagonists including adalimumab. These case reports are derived from a variety of sources including registries and spontaneous post-marketing reports.[10] Rare post-marketing cases of hepatosplenic T-cell lymphoma have been identified in patients treated with TNF-antagonists including adalimumab.[18,19] This rare type of T-cell lymphoma, has a very aggressive disease course and is usually fatal.[16] Some of the cases reported for adalimumab occurred in young adult patients with inflammatory bowel disease who were also taking other oral medications, e.g., azathioprine, that can suppress the immune system. There have also been cases of acute and chronic leukemia reported in association with the use of TNF-antagonists including adalimumab. With the current knowledge, a possible risk for the development of lymphomas or other malignancies in patients treated with a TNF-antagonist cannot be excluded.

Patients with UC and CD involving the colon have a substantially increased risk of developing colorectal cancer. The risk for colorectal cancer in CD involving the colon is similar to that of UC of similar duration and extent. Small intestinal cancer occurs at an increased rate in patients with Crohn's enteritis, but the absolute risk remains small.

Extraintestinal malignancies are uncommon in IBD but lymphomas, biliary tract cancers and squamous cell cancers of the skin may occur at an increased rate in IBD patients.[17,18]

3.1 Safety Information

Adalimumab therapy has a well established and well described safety profile based on extensive postmarketing experience and continued clinical trial patient exposure since the first approved indication in 2002 for rheumatoid arthritis. A detailed discussion of the clinical toxicology, metabolism, pharmacology and safety experience with adalimumab can be found in the current Package Insert. AbbVie is committed to continue to collect safety information including those events that may occur in this trial in order to confirm the established safety profile and to identify unknown potential adverse reactions, rare events and those events with a long latency. AbbVie is participating in an FDA-requested, TNF-inhibitor class wide exploration of the rare appearance of malignancy in patients who are 30 years of age or younger at the time of diagnosis. The risk of malignancy in this age group has not been established and is difficult to study due to its rarity. AbbVie appreciates your attention to the additional reporting requirements needed in this unlikely event, as outlined in Section 7.5 under Adverse Event Reporting.

4.0 Rationale

This protocol describes a non-interventional Registry that will evaluate the long-term safety and effectiveness of Humira as used in routine clinical practice in adult patients (18 years of age or older) with CD, who are candidates for anti-TNF therapy according to the local product label. This Registry study is part of a post-marketing commitment from AbbVie Inc. to the FDA and European Medicines Agency (EMA).

The sample size for the Registry is 5,000 patients. Recent literature data describes a lower expected rate for the adverse event of lymphoma than previous estimates; therefore, following a discussion with the FDA, the registry duration has been extended to 6 years. In addition, follow-up procedures for patients who discontinue the registry have been

added to the protocol to maximize the safety information which may be collected from all registry patients.

The participating physicians, with regard to countries and sites, are representative of the gastroenterologists who will prescribe Humira to patients with CD in North America, Europe, South Africa, New Zealand and Australia. The patients selected for this Registry correspond to the target population in the Humira labels in the participating countries. The patients will receive commercial Humira that will be prescribed per their local prescribing information.

The data collected in this Registry will be complementary to those from the pre-registration studies of adalimumab in CD. The management of the patients in this Registry reflects the current clinical practice. The participating physician is free to determine the appropriate therapy for each patient and make treatment choices as deemed clinically necessary. All patients that consent to take part in the registry will be followed for up to 6 years, providing long-term safety and effectiveness data on Humira in CD.

5.0 Registry Objective

The primary objective of this Registry is to evaluate the long-term safety of Humira in CD adult patients (18 years of age or older) who are treated as recommended in the local product label. The secondary objective is to evaluate long-term effectiveness of Humira in CD patients who are treated as recommended in the local product label.

6.0 Investigational Plan

This is a multicenter, uncontrolled non-interventional Registry of patients with CD treated in a routine clinical setting with Humira. Approximately 5,000 subjects in the US, Europe, Canada, Australia, New Zealand and South Africa will be enrolled.

Physicians will be provided with a study kit that includes a protocol, patient informed consent forms, Serious Adverse Event Report Forms, paper patient questionnaires, and electronic Case Report Forms (eCRFs).

The decision to prescribe Humira (adalimumab) to the patients should be made separately from the decision to enroll them in the Registry.

With patient consent and having met all the inclusion criteria and none of the exclusion criteria, the physician may enroll the patient into the Registry. Physicians are encouraged to treat their patients as they would in their routine clinical practice and in accordance with the local Humira (adalimumab) product label. The physician will then follow the patient during regular office visits at intervals as determined by routine clinical practice or as recommended by national guidelines.

Patient's safety data and information about medications taken for CD will be recorded on eCRFs at study enrollment and during their regularly scheduled visits which are closest to Months 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72. While the physician may deem it appropriate and necessary to have the patient return for intermediate visits during the course of the registry, data will be collected via eCRFs only at the intervals that most closely correspond to those described above.

In an effort to maximize safety data collection, physicians will be asked to do the following:

- Consent and re-enroll patients that were previously discontinued due to the prior P06-134 protocol withdrawal criteria (e.g., patient discontinued Humira). Patients that re-enroll in the Registry will resume data collection via the eCRF process as outlined in the protocol.
- For patients that re-enroll in the Registry, physicians will be asked to collect and report surgeries or hospitalizations and adverse events of special interest (Section 7.1.2) and Crohn's related medication use between registry discontinuation and re-enrollment based on a retrospective review of their patient records.

- For patients that decline re-enrollment for full safety and effectiveness data collection or who have discontinued from the Registry for other reasons, physicians will be asked to obtain the patient's consent to data release for the completion of a simplified Healthcare Provider (HCP) questionnaire on an annual basis. The first data collection period will capture data from the time of patient's discontinuation of the Registry through the start of the direct to HCP process. The questionnaire focuses on the collection of surgeries or hospitalizations and adverse events of special interest and Crohn's related medication use since registry discontinuation. The questionnaire may be completed by the registry physician or the patient's current HCP (if they are no longer under the care of a registry physician). An HCP is not considered a participating investigator in the registry since they are only completing an annual questionnaire on behalf of a former registry patient. Participating registry investigators for which all of their patients have discontinued from registry participation may convert to an HCP status if their patients(s) choose to participate in the HCP process.

If treatment with Humira is permanently discontinued for any reason, patients will be encouraged to remain in the registry or to participate in the direct to HCP process unless consent is withdrawn.

When applicable, information about the effectiveness of Humira therapy will be provided by the patients and their physician. Effectiveness of therapy provided by the patient will be collected with PROs beginning with the registry enrollment visit, at regularly scheduled visits which are closest to Months 3, 6, 9, 12, and every 6 months thereafter, if part of routine clinical assessment. The following PROs will be used: Short Inflammatory Bowel Disease Questionnaire (SIBDQ), Health Care Resource Utilization (Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalizations Questionnaire), and Work Productivity and Activity Impairment (WPAI). There are approximately 20 questions in the PRO assessments and it is expected that it will take approximately 15 minutes to complete them. Effectiveness of therapy will be collected through the Physician's Global Assessment beginning with the Registry enrollment visit and at regularly scheduled visits which are closest to Months 3, 6, 9, 12, and every

6 months thereafter, if part of routine clinical assessment. Effectiveness measures will only be collected for patients receiving Humira.

Serious adverse events (SAE) and adverse events of interest will be recorded throughout the patient's participation in the registry or direct to HCP process and/or until 70 days following discontinuation of HumiraUMIRA administration have elapsed (which ever period is longer).

Adverse events of interest for this Registry include:

- Serious opportunistic infections, e.g., invasive fungal infections and TB
- Lymphoma including hepatosplenic T-cell lymphoma; leukemia, non-melanoma skin cancer (NMSC)
- Other malignancies (excluding lymphoma, leukemia and NMSC which are recorded separately)
- Immune reactions including lupus, lupus-like reactions and serious allergic reactions
- Congestive heart failure (CHF)
- Cerebrovascular accident (CVA)
- Myocardial infarction (MI)
- CNS demyelinating disorders (including Multiple Sclerosis and Guillain-Barré syndrome)
- Hepatic events that are serious or lead to permanent discontinuation of Humira (e.g., persistent liver function test abnormalities, acute liver failure and other serious hepatic events)
- Hematologic events that are serious or lead to permanent discontinuation of Humira (e.g., Aplastic anemia, Granulocytopenia, Granulocytes maturation Arrest, Leucopenia, Neutropenia, Pancytopenia and Thrombocytopenia)
- Worsening or new onset of Psoriasis
- Vasculitis

- Diverticulitis
- Intestinal perforation
- Occurrence of symptomatic intestinal obstruction
- Events leading to premature discontinuation of HUMIRA

Information on all concomitant medications will be captured at the time of enrollment into the Registry. Information on medications taken for CD (including dose changes) and a complete list of all medications taken at the time of a serious adverse events or adverse events of interest will be collected throughout the Registry.

This is a global registry being conducted in the US, Europe, Canada, South Africa, New Zealand and Australia and as such there are multiple local product labels. In Europe, Humira is registered for patients with severe Crohn's disease, while in the other regions it is registered for patients with moderate to severe disease. This protocol has been designed to accommodate all product labels.

6.1 Physician Selection Criteria

Approximately 450 physicians will participate in this trial. Approximately 185 physicians will be included based on participation in prior clinical development studies. An additional 265 physicians will be included based on their available eligible patient population.

6.2 Selection of Study Population

Patients meeting all of the inclusion criteria and who have none of the exclusion criteria may be enrolled.

6.2.1 Inclusion Criteria

An adult patient (18 years of age or older) with CD for whom Humira therapy is indicated according to the local product label and who meet the following criteria may be enrolled in this study:

1. Patients to be enrolled must fall into one of the following categories:
    - Patients who are newly prescribed Humira therapy (have never been treated with adalimumab).
    - Patients who are current participants in AbbVie sponsored investigational CD trials, are currently receiving Humira and for whom the treating physician has made the decision to continue with Humira therapy beyond the duration of the investigational trial.
    - Patients who were prior participants in AbbVie sponsored investigational Crohn's disease trials, who have not had dose interruptions since the last dose of registry drug, where the Investigator can provide source documentation of dosing information.
    - Patients who are currently receiving Humira, as per the local product label, who have not had dose interruptions since the induction dose of Humira where the Investigator can provide source documentation of dosing information.
2. Patients willing to consent to data being collected and provided to AbbVie.
3. Patients capable of and willing to give written informed consent and to comply with the requirements of the Registry protocol.

6.2.2 Exclusion Criteria

1. Patients should not be enrolled if they cannot be treated in accordance with the local product label.

6.2.3 Patient Follow-up Criteria

In order to participate in the follow-up process, patients who discontinued the Registry must re-consent to participation in the Registry or consent to participate in the direct to HCP process.

6.3 Safety and Effectiveness Variables/Schedule of Assessments

This is a long-term Registry with the objective of documenting safety and effectiveness of Humira in routine clinical practice.

6.3.1 Safety Variables

The physician will be asked to document serious adverse events and adverse events of interest on eCRFs (Section 7.5).

Serious adverse events and adverse events of interest as defined in Section 7.1.1 and Section 7.1.2 respectively, will be reported to AbbVie from the time the physician obtains the subject's authorization to use and disclose information (or the subject's informed consent) throughout the patient's participation in the Registry, up to 6 years. In the event adalimumab therapy is interrupted, SAEs and adverse events of interest will be collected throughout the interruption. If treatment with adalimumab is permanently discontinued for any reason, patients should be encouraged to continue in the registry or the direct to HCP process for a full 6 year observation period irrespective of future treatment decisions so important safety information can be obtained, as outlined in Section 6.0.

SAE reports will be completed and submitted using an electronic version of AbbVie's standard SAE form (Section 7.5).

Additional information on the adverse events of interest will be collected on separate data collection forms. These forms will capture specific information relevant to the event of interest.

In case of pregnancy, AbbVie must be notified within 1 working day of a site's learning if a female subject becomes pregnant during the registry. No clinical data on the use of adalimumab in pregnant women is available. For details please refer to the product prescribing information. Information regarding the outcome of any pregnancy occurring in a registry patient will be collected (Section 7.6). Patients who become pregnant and interrupt their Humira (adalimumab) therapy may remain in the Registry.

6.3.2 Effectiveness Variables

Information to evaluate the effectiveness of adalimumab therapy will be collected from patients and their physicians if part of routine clinical assessment. In the event adalimumab therapy is interrupted, effectiveness variables will be collected during the interruption.

The effectiveness of therapy evaluation provided by the subject will be collected with PROs beginning with the study enrollment visit, at regularly scheduled visits which are closest to Months 3, 6, 9, 12, and every 6 months thereafter, if part of routine clinical assessment. The following PROs will be used:

- SIBDQ,
- Health Care Resource Utilization (Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalizations Questionnaire),
- WPAI.

There are approximately 20 questions in the PRO assessments and it is expected that it will take approximately 15 minutes to complete them.

Effectiveness of therapy provided by the study physician will be collected through the Physician's Global Assessment, if part of routine clinical assessment. The following assessments will be collected:

- General Well Being,

- Abdominal Pain,
- Diarrhea,
- Blood in Stool,
- Abdominal Mass,
- Crohn's Disease Related Complications.

6.4 Study Procedures

The following procedures will be performed during the study at the time points specified in Table 1, Schedule of Study Assessments.

Table 1. Schedule of Study Assessments

Procedure	Study Enrollment	Month[a] 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72	At Time of Reported Event
Informed Consent	√		
Demographics	√		
Medical/Surgical Hx (including Crohn's Medical/Surgical Hx)	√		
Safety Data Collection (AEs of Interest/SAEs)	√	√	√
Previous Crohn's Disease Medications, prior concomitant medications	√		
Prior and Concomitant CD Medications	√	√	√
All Concomitant Medications	√		√
Physician Global Assessment	√	√	
SIBDQ	√	√	
WPAI (Work Productivity Activity Impairment) Questionnaire	√	√	
Healthcare Resource Utilization (Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalizations Questionnaire)	√	√	
Adalimumab Treatment and Dosing Changes	√	√	
Case Report Form Completion	√	√	√

a. Data collection at regular visits that are closest to time points described. For patients participating in the HCP questionnaire process, follow-up is annually and events of interest, surgeries, hospitalizations and medications taken for CD are collected.

6.4.1 Informed Consent

All patients will provide consent for release of their information to AbbVie (Sponsor) on an informed consent form, which can be modified according to local requirements that is signed and dated by the subject prior to the release of any such information to the Sponsor. Before informed consent is obtained, the physician or designee will explain to the patient the nature and purpose of the study and the data to be provided to the Sponsor. After the informed consent form is signed, the original informed consent form will be

placed in the subject's medical record and a signed copy should be given to the patient. Registry physicians will be asked to re-consent patients discontinued due to the Amendment 1 P06-134 protocol withdrawal criteria. Patients that decline re-enrollment or who have discontinued from the registry for other reasons, will be asked to consent to the direct to HCP process for registry data collection.

6.4.2 Demographics

The physician will obtain patient demographic information at the study enrollment visit and record it on the Enrollment eCRF. The demographic information will include date of birth, gender, race, ethnicity, and subject initials where local law permits. Patients rolling over from a previous adalimumab clinical study will have their subject number form the previous study captured in the Enrollment eCRFs.

6.4.3 Medical History

A complete non-Crohn's related medical and surgical history as well as history of tobacco and alcohol use, will be obtained from each patient at study enrollment. Additionally, information about each patient's specific Crohn's related medical and surgical history will be recorded.

The location(s) of the patient's Crohn's disease will be recorded in the source documents and on the appropriate eCRF pages (gastroduodenal, ileum, jejunum, colon, rectum, anal, and/or perianal) [more than one location can be selected, as appropriate]. History should also include duration of the disease and/or history of complications related to the disease.

6.4.4 Safety Data Collection

The following safety information will be collected: adverse events of interest and serious adverse events as defined in Section 7.0. The description of the event, the date of onset, severity, time course, duration, outcome (when known), relationship of the adverse event to adalimumab, information specific to the event, an alternate etiology for events not considered "probably related" to adalimumab, final diagnosis/syndrome (if known), and

any action(s) taken. Information about all medications taken at the time of the SAE or an adverse event of interest, including the medications to treat the event, will be collected.

6.4.5 Prior and Concomitant Medications

Any previous medications (corticosteroids, aminosalicylates, anti-TNF drugs including commercial Humira, immunosuppressants [i.e., azathioprine, 6-mercaptopurine, methotrexate] and antibiotics) used to treat CD will be captured at the study enrollment visit. Information on the highest maintained dose, date of last administration, length of time on the medication and reason for stopping the CD medication will be collected in the source documents and appropriate eCRF pages.

All concomitant medications the subject is receiving at the Registry enrollment visit should be recorded in the source documents and on the appropriate page of the eCRF along with the reason for use, duration of use and dosages. Information on medications taken for CD (including dose changes) and a complete list of all medications taken at the time of a serious adverse event or adverse events of interest will be collected throughout the Registry.

For patients who are enrolled in the Registry, after the initiation of Humira therapy, all concomitant medication changes from the initiation of Humira therapy until enrollment into the Registry will need to be captured.

In addition, for patients age ≤ 30 with a reported malignancy adverse event, prior exposure to, or current use of, antineoplastics, or other drugs which have a risk of malignancy as stated in their label and other relevant dosing information to estimate total exposure will be collected in the source documents and appropriate eCRF pages. At the time of the reported malignancy adverse event, sites will be asked if any of the prior and concomitant medications contributed to the event. Any medications used prior to the study will be captured on the appropriate eCRF. Information on the reason for use, date(s) of administration including start and end dates, highest maintained dose, dosage

information including dose, route and frequency, and reason for stopping the medication will be collected in the source documents and appropriate eCRF pages.

The administration of anakinra (Kineret®) or other biologic agents may not be given concurrently while on Humira. Please refer to your local product label for information regarding the use of live vaccines while a patient is on Humira.

The Study Designated Physician identified in Section 7.5 should be contacted if there are any questions regarding prior or concomitant medications.

After registry enrollment, patients should not be enrolled into any interventional clinical trial.

AbbVie will not provide any medication or therapy for this Registry.

6.4.6 Physician Global Assessment

A Physician Global Assessment will be calculated at all Registry visits starting at study enrollment, if part of the physician's routine clinical assessment. The complication of "draining fistula," shall mean any fistula present at an exam that is draining upon gentle compression or as determined by the investigator.

The calculation of the Physician Global Assessment is located in Appendix F.

6.4.7 Outcomes and Questionnaires

The patient will complete the SIBDQ and WPAI Questionnaires at all study visits starting at Registry enrollment, if part of the physician's routine clinical assessment. Patients will complete the questions directly on the eCRFs that will be considered source documents. A copy of the SIBDQ is located in Appendix C. A copy of the WPAI is located in Appendix E.

The Healthcare Resource Utilization form (Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalizations Questionnaire) will be completed by site staff starting at

study enrollment, if part of the physician's routine clinical assessment. Only patients who have previously been enrolled in an adalimumab clinical trial will have this questionnaire completed at Registry Enrollment.

A copy of the questionnaire is located in Appendix D.

6.4.8 Adalimumab Treatment and Dosing Changes

The participating physician will provide the patient a prescription for HUMIRA, along with instructions for appropriate use. At subsequent protocol-defined study visits the physician will collect the start and stop dates, any dose interruptions and reason for the dose interruption that may have occurred since the last study visit. The dose, dates of administration, any dose interruptions and the reason for the interruption will be captured in the source documents and eCRFs.

Dose interruptions for the study will be defined as patients missing > 1 dose. The reason(s) for interruptions will be captured on the eCRF.

Most clinical data associated with this study will be collected and reported electronically (eCRF) via a web address and secure password. Patient questionnaires will be completed on forms formatted for fax scanning. The site will fax or email completed forms into the designated Study Help Desk.

At the enrollment visit, the physician will complete the Enrollment eCRFs by obtaining and recording all available required information, including visit date, demographic data, concomitant diseases and concomitant medications.

At subsequent visits corresponding to the schedule of assessments (Table 1), the physician will complete the appropriate eCRF by obtaining and recording all available information. Since this is an observational study conforming to usual clinical practice, data from subject visits that most closely correspond to the schedule of assessment at Months 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, 60 66 and 72 will be accepted. For example, if a patient visits the physician's site at Month 5, this is close to the protocol-defined 6-month study

visit, so data can be collected for this visit. If the same patient unexpectedly returns for a visit to the physician's site at a date closer to the 6-month visit, no further PRO data needs to be collected since the data was previously collected. Safety data that meets the criteria for collection should be collected regardless of protocol-defined study visits.

If a patient completes the 6-year observation period study completion of eCRFs should be completed.

6.5 Withdrawal of Patients from Registry

A patient may withdraw from the registry at any time without prejudice. If the physician, for any reason, decides it is in the best interest of the patient to permanently discontinue Humira, treatment should be stopped but the patient should be encouraged to continue in the registry so important and complete safety information can be obtained, as outlined in Section 6.0. If a patient withdraws or is lost to follow up, such should be noted, along with the reason for withdrawal on the study completion eCRF.

Patients who were discontinued from the registry due to prior protocol withdrawal criteria (i.e., patients who have discontinued Humira therapy) or discontinued for other reasons will be contacted to determine interest in re-enrollment into the registry or completion of a simplified HCP questionnaire on an annual basis.

All patients that are unreachable after three documented attempts to contact the patient via phone, email, or certified letter, will be considered lost to follow-up.

AbbVie will take reasonable actions to ascertain vital status at the end of the patient's 6-year observational period. AbbVie will make every effort to work through investigational sites to match patients lost to follow-up against the National Death Index (NDI) in the US, national/regional cancer registries and vital registries as available in other countries and were allowed per local regulations.

6.6 Study Management

AbbVie, working in cooperation with REGISTRAT-MAPI, will manage the study, collect all study information via eCRFs and PROs, and complete statistical analyses of the study.

7.0 Adverse Events/Adverse Event Reporting

The physician will monitor each patient for serious adverse events and adverse events of interest throughout the patient's participation in the registry or direct to HCP process, and/or until 70 days following discontinuation of Humira administration have elapsed (whichever period is longer). The physician will assess and record any serious adverse event and adverse events of interest in detail including the date of onset, description, severity, time course, duration and outcome (when known), relationship of the adverse event to drug, an event diagnosis, if known, and any action(s) taken. For SAEs not considered "probably related" to registry drug, the physician will provide another cause of the event. Serious adverse events or adverse events of interest, whether in response to a query, observed by site personnel, or reported spontaneously by the patient will be recorded. Information about any concomitant medications taken at the time of the SAE or the adverse events of interest will be collected. For all adverse events of interest, the physician must pursue and obtain all the above mentioned information in order to adequately determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE as well as to determine a causal relationship.

7.1 Definitions

7.1.1 Adverse Events

An AE is defined as any untoward medical occurrence that occurs during treatment in a patient, but does not necessarily have a causal relationship with their treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not the event is considered causally related to the use of the product.

Such an event can result from use of the drug as stipulated in the labeling, as well as from accidental or intentional overdose, drug abuse, or drug withdrawal. Any worsening of a pre-existing condition or illness is considered an AE.

An elective surgery/procedure scheduled to occur during the registry will not be considered an SAE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure was planned prior to entry into the registry. However, if the pre-existing condition deteriorates unexpectedly during the registry (e.g., surgery performed earlier than planned) then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

7.1.2 Adverse Events of Interest

The physician will monitor each patient for clinical and laboratory evidence for adverse events of interest at the Baseline visit and on a routine basis throughout the registry.

Adverse events of interest for this registry include:

- Serious opportunistic infections e.g., invasive fungal infections and TB
- Lymphoma including hepatosplenic T-cell lymphoma; leukemia, non-melanoma skin cancer (NMSC)
- Other malignancies (except lymphoma, leukemia and NMSC)
- Immune reactions including lupus, lupus-like reactions and serious allergic reactions
- Congestive heart failure (CHF)
- Cerebrovascular accident (CVA)
- Myocardial infarction (MI)
- CNS demyelinating disorders (including Multiple Sclerosis and Guillain-Barré syndrome)

- Hepatic events that are serious or lead to permanent discontinuation of Humira (e.g., persistent liver function test abnormalities, acute liver failure and other serious hepatic events)
- Hematologic events that are serious or lead to permanent discontinuation of Humira (e.g., Aplastic anemia, Granulocytopenia, Granulocytes maturation Arrest, Leucopenia, Neutropenia, Pancytopenia and Thrombocytopenia)
- Worsening or new onset of Psoriasis
- Vasculitis
- Diverticulitis
- Intestinal perforation
- Occurrence of symptomatic intestinal obstruction
- Events leading to premature discontinuation of Humira

During the course of the registry additional adverse events of interest may be identified by AbbVie. Updates to the adverse events of interest will be maintained and collected through the eCRF system. Sites will be trained on all updates to the eCRF system.

The physician will assess and record any additional information on the adverse event of interest in detail on the Adverse Events of Interest eCRF.

The physician will assess all reported adverse events of interest for seriousness and follow the requirements/timelines for reporting any AEI that fulfills the criteria of an SAE, as defined in Section 7.1.3.

7.1.3 Serious Adverse Events

If an adverse event meets any of the following criteria, it is to be reported to AbbVie as a serious adverse event within 24 hours of notification of the study site:

Death of Subject	An event that results in the death of a subject.
Life-Threatening	An event that, in the opinion of the Investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization	An event that occurs while the study subject is hospitalized and prolongs the subject's hospital stay.
Congenital Anomaly	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity	An event that results in a condition that substantially interferes with the activities of daily living of a study subject. Disability is not intended to include experiences of relatively minor medical significance such as headache, nausea, vomiting, diarrhea, influenza, and accidental trauma (e.g., sprained ankle).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the subject and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of subject, life-threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Examples of such events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
Spontaneous Abortion	Miscarriage experienced by study subject.
Elective Abortion	Elective abortion performed on study subject.

7.2 Adverse Event Severity

The physician will use the following definitions to rate the severity for any adverse event of interest being collected as an endpoint/datapoint in the registry and for all serious adverse events:

Mild	The adverse event is transient and easily tolerated by the subject.
Moderate	The adverse event causes the subject discomfort and interrupts the subject's usual activities.
Severe	The adverse event causes considerable interference with the subject's usual activities and may be incapacitating or life-threatening.

7.3 Relationship to Pharmaceutical Product

The physician will use the following definitions for any adverse event of interest being collected as an endpoint/datapoint in the registry and for all serious adverse events, to assess the relationship of the adverse event to the use of the pharmaceutical product:

Probably Related	An adverse event has a strong temporal relationship to registry drug or recurs on re-challenge and another cause of event is unlikely or significantly less likely.
Possibly Related	An adverse event has a strong temporal relationship to the registry drug and another cause of event is equally or less likely compared to the potential relationship to registry drug.
Probably Not Related	An adverse event has little or no temporal relationship to the registry drug and/or a more likely other cause of event exists.
Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the registry drug (e.g., has no temporal relationship to registry drug or has a much more likely other cause of event).

For serious adverse events and adverse events of interest, if a Physician's opinion of possibly, probably not, or not related to Humira is given, another cause of event must be provided by the physician for the SAE or adverse event of interest.

7.4 Adverse Event Collection Period

Serious adverse events and adverse events of interest will be reported to AbbVie from the time the physician obtains the subject's initial authorization to use and disclose information (or the subject's informed consent) throughout the patient's participation in the Registry, or direct to HCP process, and/or until 70 days following discontinuation of Humira administration have elapsed (whichever period is longer). A medical event that occurs after a patient discontinues the registry that is considered to be related to the patient's exposure to Humira will be reported via standard post-marketing reporting practices.

In the event Humira therapy is interrupted, SAEs and adverse events of interest will be collected throughout the interruption. If treatment with adalimumab is permanently discontinued for any reason, the reason will be recorded and the patients should be encouraged to remain in the registry for the full 6 years so important safety information can be obtained.

7.5 Adverse Event Reporting

In the event of an SAE, and/or additionally, any nonserious event of malignancy in patients 30 years of age and younger, whether related to Humira or not, the physician will notify the AbbVie Immunology Clinical Safety Management Team within 24 hours of the physician becoming aware of the event by entering the serious adverse event and/or nonserious event of malignancy in patients 30 years of age and younger data into the electronic data capture (EDC) system.

Serious adverse events and nonserious events of malignancy in patients 30 years of age and younger, that occur prior to the site having access to the EDC system should be faxed to the AbbVie Immunology Clinical Safety Management Team within 24 hours of being made aware of the adverse event.

If the EDC system is unavailable, the completed Serious Adverse Event Form should be submitted via fax:

FAX to: +1 (847) 785-8227

For SAE concerns, contact the Immunology Safety Team at:

Immunology Safety Team
AbbVie
Dept. R477, Bldg. AP4-2
1 North Waukegan Road
North Chicago, IL 60064

Safety Hotline: +1 (847) 938-8737
Fax: +1 (847) 785-8227
Email: GPRD SafetyManagement Immunology@abbvie.com

For any subject safety concerns, please contact the physician listed below:

AbbVie Safety and Medical Contact			
Name/Function	**Address**	**Phone/Fax**	**Email**
Majin Castillo, Associate Medical Director	Global Pharmaceutical Research and Development 1 North Waukegan Road North Chicago, IL 60064	Phone: +1-847-935-2495 Fax: +1-847-936-5845 Mobile: +1-224-475-5591	Majin.castillo@abbvie.com

7.6 Pregnancy

Pregnancy in a registry patient must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Pregnancies will be collected from the date of the first dose through 150 days following the last dose of registry dose.

Physicians should refer to their local prescribing information when making treatment decisions for patients who become pregnant while being treated with Humira in the Registry. Patients who become pregnant and interrupt their Humira therapy should

remain in the registry and should continue to be monitored for new SAEs and adverse events of Interest.

All female patients who become pregnant while enrolled in the registry will be followed from the time of pregnancy is reported until the outcome of the pregnancy is known. Information regarding a pregnancy occurrence in a registry patient and the outcome of the pregnancy will be collected.

Pregnancy in a registry patient is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

7.7 Data Collection Procedures for Patients Who Re-enroll in the Registry

For patients who re-enroll in the registry, registry physicians will document any hospitalizations, surgeries, and any adverse event of interests as defined in Section 7.1.2. The physician will assess and record the date of onset (where known) and description of the event. These events will be reported via eCRF from the time of initial registry discontinuation through the date of re-enrollment, irrespective of any treatment interruption, any changes in treatment, or discontinuation of adalimumab.

The use of other medications used to treat CD and the stop and the restart dates for Humira, as applicable, from the time of initial registry discontinuation through the date of re-enrollment will be collected.

Effectiveness data will not be collected during the timeframe when the patient was not participating in the registry.

For visits occurring after re-enrollment, registry physicians will resume data collection in the eCRF process as outlined in the protocol. The duration of follow-up includes the time from initial registry consent up to 6 years.

7.8 Data Collection Procedures for Patients Who Participate in the Direct to HCP Process

For patients participating in the direct to HCP process, HCPs will document any hospitalizations or surgeries and any adverse event of interest as defined in Section 7.1.2 annually via a paper questionnaire or EDC. The HCP will assess and record the date of onset (where known), and description of the event. The use of other medications used to treat CD, and the start and stop dates for Humira will be collected on an annual basis.

These events will be reported to AbbVie from the time of initial registry consent up to 6 years, irrespective of any treatment interruption, any changes in treatment, or discontinuation of adalimumab.

Effectiveness data will not be collected as part of the direct to HCP process.

8.0 Ethics and Quality

Prior to any registry-related data being collected, the informed consent statement will be reviewed and signed and dated by the patient and the person who administered the informed consent. A copy of the signed informed consent form will be given to the patient and the original will be placed in the patient's medical record. A patient informed consent template will be provided to the registry physician. A copy of the patient signed informed consent or data release form (as applicable) will be provided to the HCP.

8.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

Should the institution/affiliation require an institutional review board approval/ notification of this protocol (and related informed consent), it shall be the physician's responsibility to secure such approval prior to initiating any study procedures.

8.2 Quality Assurance

Prior to the initiation of the study, an Investigator's meeting will be held with AbbVie personnel, the investigators and their study coordinators, the Registrat's project manager and the CRAs for the study. This meeting will include a detailed discussion of the protocol, performance of study procedures and paper and eCRF completion. In addition to or instead of the Investigator's meeting, the personnel at each registry site may be trained on the study procedures by a CRA at a study initiation visit via the telephone or on-site and will be given a paper and eCRF completion workbook for reference.

Approximately ten percent (10%) of the registry sites will be monitored on-site for the study. At each site selected for a visit, one hundred percent (100%) source document review for SAEs, adverse events of interest and dose interruption data will be performed against entries on the paper and eCRF and a quality assurance check will be performed to ensure that the physician is complying with the protocol and local regulations. The monitoring plan will detail how sites will be selected for the on-site monitoring visits. Throughout the study, Registrat-MAPI and AbbVie will periodically follow-up with the sites to ensure that SAEs and adverse events of interest are being reported.

All registry data will be entered in the study via the eCRF and the fax scan of paper PRO (Patient Reported Outcome) forms. All eCRF information will be imported directly into the electronic data capture system. Paper PRO forms are first quality controlled checked and then entered into the electronic data capture system. All other paper questionnaires (e.g., direct to HCP questionnaire) will be entered into the database on an annual basis. Any necessary corrections will be made to the database and documented via addenda, queries, source data clarification form or audit trail. A manual review of selected line listings will also be performed at the end of the study.

9.0 Source Documents and Case Report Form Completion

9.1 Source Documents

Source documents are defined as original documents, data and records. This may include hospital records, clinical and office charts, laboratory data/information, pharmacy dispensing and other records, recorded data from automated instruments, microfiches, photographic negatives, microfilm or magnetic media, and/or x-rays. Data collected during this study must be recorded on the appropriate source documents. The only exception will be for patient-completed questionnaires (SIBDQ and WPAI). There will be no corresponding source documentation as the subject completes the forms directly on the CRF.

The Registry Physician(s)/institution(s) will permit study-related monitoring, audits, IEC/IRB review, and regulatory inspection(s), providing direct access to source data documents.

9.2 Case Report Forms

All data associated with this registry will be collected and reported electronically (eCRF) via a web address and secure password. Patient self-administered questionnaires will be completed on paper forms and then submitted to be entered into the database.

At the Enrollment visit, the physician will complete the Enrollment eCRFs by obtaining and recording all available required information, as outlined in Section 6.4.

At subsequent visits corresponding to the schedule of assessment (Table 1), the physician will complete the appropriate eCRF by obtaining and recording all available information. Since this is an observational registry conforming to usual clinical practice, data from patient visits that most closely correspond to the recommended schedule of assessment at Months 3, 6, 9, 12, 18, 24, and every 6 months through the end of registry participation will be collected.

Paper questionnaires will be generated for patients that decline re-enrollment to participation in the Registry or who have discontinued from the Registry for other reasons, and consent to data release for the completion of a simplified HCP questionnaire in the direct to HCP process. Completed questionnaires will be entered into the database on an annual basis.

Upon completion of or termination from the registry, all patients should have study completion eCRFs completed as well as an assessment of their current medical conditions.

10.0 Statistical Methods and Determination of Sample Size

10.1 Statistical and Analytical Plans

Analyzable Populations:

Safety Populations During the Registry:

The Registry Safety Population consists of all patients who received at least one dose of Humira (adalimumab) in the Registry. This will be the population for safety analyses in the Registry and include safety data collected during the Registry only.

The "Episodic Dosing" Population will consist of patients in the Registry Safety Population who:

- discontinue Humira (adalimumab) at least once for more than 70 days and receive at least one dose of adalimumab after the treatment interruption,
- do not receive any other biologics during the treatment interruption and,
- provide data before and after Humira (adalimumab) treatment interruption period(s)
- and include safety data collected during the Registry only.

For patients previously treated with commercial Humira before enrollment into the Registry, Day 1 of adalimumab treatment will be the 1st day of Humira therapy, i.e., before enrollment into the Registry. Detailed information on concomitant medications, safety and effectiveness between the 1st dose of Humir and enrollment into the Registry will be available for these patients.

Re-enrollment Safety Population:

The Re-enrollment Safety Population consists of all patients who were discontinued from the Registry due to prior protocol withdrawal criteria (i.e., patients who have discontinued Humira therapy) or discontinued for other reasons and re-consent to participation in the Registry. This will be the population for safety analyses of data collected during the re-enrollment period.

For patients that re-enroll in the Registry, safety information collected between registry discontinuation and re-enrollment based on a retrospective review of their patient records will be analyzed separately.

HCP Safety Population:

The HCP Safety Population consists of all patients that decline re-enrollment to participation in the Registry or who have discontinued from the Registry for other reasons and consent to data release for the completion of a simplified HCP questionnaire in the direct to HCP process. This will be the population for safety analyses of data collected on HCP questionnaire.

10.2 Planned Methods of Statistical Analysis

Descriptive statistics are to be provided for demographic, effectiveness, and safety parameters. Continuous variables will be summarized by the number of observations, mean, standard deviation, 1st quartile, median, 3rd quartile, minimum, and maximum; whereas discrete variables will be summarized by counts and percentages. All analyses

will be performed on the Safety Population in the Registry that includes all patients who receive at least one dose of adalimumab unless otherwise specified.

10.3 Demographics and Registry Enrollment Characteristics

Demographic and Registry enrollment characteristics will be summarized.

The following covariates will be measured to assess their influence on the primary and secondary endpoints: age (years), sex, race/ethnicity, smoking history, duration of CD, severity of CD (as measured by Physician Global Assessment, WPAI and SIBDQ), prior therapies for CD, concomitant CD medications, co-morbid conditions, and adalimumab dosage and exposure duration.

10.4 Effectiveness Analyses

Effectiveness parameters measured over the course of registry, include change from registry enrollment in the following measures: SIBDQ, Health Care Resource Utilization, WPAI, and Physician's Global Assessment.

The Physician's Global Assessment and SIBDQ scores will be summarized descriptively at each Registry visit. Additionally, changes from Registry enrollment by Registry visit will also be summarized for these outcomes using descriptive statistics. Health Resource Utilization and WPAI will also be summarized with descriptive statistics at each Registry visit.

For efficacy analyses of the "episodic dosing" population, only patients providing evaluations of efficacy at the two timepoints described below will be considered:

- data prior to the interruption in dosing, specifically at/after 12 weeks from enrollment in the Registry study.
- data after the dosing interruption is over, specifically, at/after 12 weeks upon resumption of Humira. For these patients, efficacy data at/after 12 weeks of

the 1st treatment in the Registry and at/after 12 weeks after the restart of Humira treatment during the Registry study will be summarized.

10.5 Safety Analyses

For the Registry Safety Population, treatment-emergent SAEs and adverse events of interest will be summarized. Treatment-emergent SAEs and adverse events of interest are defined as: (1) new events that begin either on or after the first dose of Humira through the last dose of Humira plus 70 days; or (2) increase in severity of ongoing SAEs that had occurred before the first dose date of Humira. The number and percent of patients experiencing SAEs and adverse events of interest will be tabulated by body system and Medical Dictionary for Drug Regulatory Activities (MedDRA®) preferred term. The percent of patients will be presented with 95% confidence intervals. In addition, summary of SAEs and adverse events of interest by severity and relationship to registry drug will be presented.

The event rate of SAEs and of each adverse event of interest per 100 patient year of observation will be presented. Event rates will be presented with 95% confidence intervals. For patients enrolled from a prior CD study, the total number of SAEs and adverse events of interest will include the events reported during their participation in the previous study plus any events reports during the Registry.

In addition, Observational AEs: SAEs and AEs of interest occurring from the first dose of Humira in the registry through the last contact including re-enrollment period and during the HCP process will be tabulated.

For the 'Episodic Dosing' Population, following analyses will be provided:

- Summary of SAEs and AEs of special interest will be provided for patients with episodic dosing and without episodic dosing.

- Summary of SAEs and AEs of special interest will be provided before the treatment interruption and after the treatment interruption for patients with episodic dosing.
- For each SAE and AE of special interest, and each episodic dosing, a shift table to summarize number and percentage of patients who have the event or not before the treatment interruption and after the treatment interruption.

For the Re-enrollment Safety Population, the number and percent of patients experiencing SAEs and AEs of interest during the re-enrollment period will be tabulated by body system and MedDRA preferred term. In addition, the number and percent of patients experiencing SAEs and AEs of interest collected between registry discontinuation and re-enrollment based on a retrospective review of their patient records will be tabulated separately.

For HCP Safety Population, the number and percent of patients experiencing SAEs and AEs of interest collected on HCP questionnaire during the HCP process will be tabulated by body system and MedDRA preferred term.

10.6 Interim Analyses

Analyses will be completed periodically, and at the end of the Registry, on all cumulative data at specific time points. The timing and content of the interim analyses will be based on commitments made globally to regulatory agencies, from the Steering Committee meetings and the Publication Plan.

10.7 Determination of Sample Size

The proposed sample size for this Registry is 5,000 patients. The sample size was calculated based on the following assumptions:

The general population has an expected lymphoma rate of 0.0263 per 100 patient year (PY), based on lymphoma rates in the SEER 17 Registry database for ages 15 to 76[20] sex-adjusted to match the Crohn's disease population which is 60% female. Assuming a

lymphoma rate four times higher than the general population rate for Crohn's disease patients previously exposed to IS therapy, 73% of the CD Registry patients would have an expected background rate of 0.1052 per 100 PY, and the remaining 27% of non-IS exposed patients would have an expected background rate of 0.0263 per 100 PY. Therefore, the overall population of patients enrolled in the CD Registry would have an expected background lymphoma rate of 0.084 events per 100 PY (based on the weighted average of the two rates, i.e., 73%*0.1052 + 27%*0.0263 = 0.084/100 PY).

The Poisson distribution was applied as the appropriate methodology[21] for the sample size calculation. Based on an event rate of p_1 = 0.084/100 PY to allow to reject the null hypothesis H_0 that the observed event rate is more than double the event rate of 0.084/100 PY (p_0 = 0.168/100 PY) in favor of the alternative hypothesis H_a with a one-sided type I error rate of α = 5% and power 90% (type II error α = 10%), the required patient years (n) and events (x_0) would meet the following criteria:

- Type I error

$$\alpha = \sup_{H_0}(P(X \le x_0)) = P_{p=p_0}(X \le x_0) = \sum_{k=0}^{x_0} \frac{\exp(-np_0)(np_0)^k}{k!} < 0.05$$

- Power

$$1-\beta = \inf_{H_a}(P(X \le x_0)) = P_{p=p_1}(X \le x_0) = \sum_{k=0}^{x_0} \frac{\exp(-np_1)(np_1)^k}{k!} >= 0.9$$

- The upper bound of the 100(1-α)% confidence interval for the event rate at given x_0 for the Poisson distribution

$$\frac{\chi^2_{2(x_0+1);\alpha}}{2n} < p_0 = 0.168/100PY$$

The calculation yields that 15,180 total patient years or 17 events will be needed to provide 90% power to detect a doubling of the risk of lymphoma events at one-sided type I error rate of $\alpha = 5\%$.

The attrition rates were estimated using the final data from the two Crohn's disease long-term clinical trials (Studies M02-433 and M04-690) resulting in a KM estimated median time to dropout of 3 years (1,093 days). Using the exponential attrition rate function of $R(t) = 1 - e^{-\lambda * t}$, this corresponds to an estimated $\lambda = 0.231$. The cumulative patient years over [0, 6] years can be calculated by:

$$yr = \int_0^6 e^{-0.231*t} dt = 3.246$$

With 5,000 patients, the total patient years over the 6 years follow-up period will be 5000*3.246 = 16230. The total of 16,230 patient years exceeds the 15,180 total patient years calculated above to detect a doubling of the risk of lymphoma events.

11.0 Use of Information and Publication

11.1 Use of information

All information concerning adalimumab and AbbVie's operations, such as AbbVie's patent applications, formulas, manufacturing processes, basic scientific data, or formulation information, supplied by AbbVie and not previously published is considered confidential information.

The information developed during the conduct of this Registry is also considered confidential and will be used by AbbVie in connection with the development of adalimumab. This information may be disclosed as deemed necessary by AbbVie to other investigators, other pharmaceutical companies, to the FDA and to other regulatory agencies. To allow for the use of the information derived from this Registry and to ensure complete and thorough analysis, the Investigator is obligated to provide AbbVie with

complete test results and all data developed in this Registry and to provide direct access to source data/documents for study-related monitoring, audits, IEC/IRB review, and regulatory inspection.

This confidential information shall remain the sole property of AbbVie, shall not be disclosed to others without the written consent of AbbVie, and shall not be used except in the performance of this Registry.

The physician will maintain a confidential patient identification code list of all patients enrolled in the Registry (by name and subject number). This list will be maintained at the site and will not be retrieved by AbbVie.

11.2 Final Report and Publication

At the end of the registry, a final registry report will be written. This report will contain a description of the objectives of the registry, the methodology of the registry and its results and conclusions. The completed CRFs, questionnaires, and the registry report must be treated as the confidential property of AbbVie and may not be released to unauthorized people in any form (publications or presentations) without express written approval from AbbVie. The results of this registry may be published by AbbVie or by any one of the participating physicians after agreement with AbbVie.

All information concerning adalimumab and AbbVie's operations, such as patent applications, formulas, manufacturing processes, basic scientific data, or formulation information supplied by AbbVie which have not been previously published are considered confidential by AbbVie and shall remain the sole property of AbbVie. The physician agrees to use this information only to perform this Registry and will not use it for other purposes including publications and presentations without AbbVie's written consent.

It is understood by the physician that the information developed in the Registry will be used by AbbVie in connection with the development of adalimumab and, therefore, may be disclosed as required to other clinical investigators, other pharmaceutical companies, to

the US FDA and to other regulatory agencies. It is understood that there is an obligation to provide AbbVie with complete test results and all data resulting from this Registry and to provide direct access to source data/documents for Registry related monitoring, audits, IEC/IRB review, and regulatory inspection.

11.3 Internet Sites

Information regarding this Registry may be posted on various internet web sites and will maximally include study name, number, general population to be enrolled, entrance qualifications, brief description, objectives, doses, accruing investigators (upon their approval) and number of patients to be enrolled.

12.0 Completion of the Registry

The physician will conduct this registry in compliance with the protocol and all applicable regulatory and legal requirements. AbbVie may terminate this registry at any time, either in its entirety or at a site, for reasonable cause provided that written notice is submitted at a reasonable time in advance of the intended termination. The physician may also terminate the registry at their site for reasonable cause, after providing written notice to AbbVie within a reasonable time in advance of the intended termination. The end-of-registry is defined as the date of the patient's last visit in the registry or the HCP process, whichever occurs later.

13.0 Physician's Agreement

1. I have reviewed the local prescribing information for Humira (adalimumab).

2. I have read this protocol and agree that the study is ethical.

3. I agree to conduct the study as outlined and in accordance with all applicable regulations and guidelines.

4. I agree to maintain the confidentiality of all information received or developed in connection with this protocol.

Protocol Title:	A Long-Term Non-Interventional Registry to Assess Safety and Effectiveness of HUMIRA® (Adalimumab) in Subjects with Moderately to Severely Active Crohn's Disease (CD)
Protocol Date:	18 June 2013

Signature of Principal Investigator — Date

Name of Principal Investigator (printed or typed)

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Appendix A. List of Abbreviations and Definition of Terms

Abbreviations

AE	Adverse event
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CRO	Contract Research Organization
DMARD	Disease Modifying Antirheumatic Drug
CRF	Case Report Form
eCRF	Electronic Case Report Form
EOW	Every Other Week
EU	European Union
FDA	Food and Drug Administration
HBV	Hepatitis B Virus
HCP	Health Care Provider
HIV	Human Immunodeficiency Virus
IEC	Independent Ethics Committee
IgG	Immunoglobulin
IL	Interleukin
IRB	Institutional Review Board
ITT	Intent To Treat
MP	Mercaptopurine
MTX	Methotrexate
PMOS	Post-Marketing Observational Study
PPI	Product Package Insert
PRO	Patient Reported Outcome
Ps	Psoriasis
PsA	Psoriatic arthritis
PY	Patient Years
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
SC	Subcutaneous
SIBDQ	Short Quality of Life in Inflammatory Bowel Disease Questionnaire
TB	Tuberculosis

TDRF	Termination Data Report Form
TNF	Tumor Necrosis Factor
UC	Ulcerative colitis
US	United States
WPAI	Work Productivity and Activity Impairment

Appendix B. List of Protocol Signatories

Name	Title	Functional Area
Majin Castillo	Associate Medical Director	Clinical
Suzanne Green	Medical Director Deputy – EU Qualified Person for Pharmacovigilance	Pharmacovigilance
Natalia Kan-Dobrosky	Senior Statistician	Statistics
Holly Read	Senior Medical Director	Pharmacovigilance
Roopal Thakkar	Project Director	Clinical
Natalie Tolli	Senior Director	Regulatory Affairs
Marilyn Wanca	Clinical Research Manager Associate	Clinical

Appendix C. Short Quality of Life in Inflammatory Bowel Disease Questionnaire (SIBDQ)

The Inflammatory Bowel Disease Questionnaire (IBDQ), authored by Dr. Jan Irvine et al, is the copyright of McMaster University (Copyright ©1989, McMaster University). The IBDQ has been provided under license from McMaster University and must not be copied, distributed or used in any way without the prior written consent of McMaster University.

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.

1. How often has the feeling of fatigue or of being tired and worn out been a problem for you during the last 2 weeks? Please indicate how often the feeling of fatigue or tiredness has been a problem for you during the last 2 weeks by picking one of the options from (Systemic)
    - All of the time
    - Most of the time
    - A good bit of the time
    - Some of the time
    - A little of the time
    - Hardly any of the time
    - None of the time

2. How often during the last 2 weeks have you had to delay or cancel a social engagement because of your bowel problem? Please choose an option from (Social)

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- Hardly any of the time
- None of the time

3. How much difficulty have you had, as a result of your bowel problems, doing leisure or sports activities you would have liked to have done during the last 2 weeks? Please choose an option from (Social)

- A great deal of difficulty; activities made impossible
- A lot of difficulty
- A fair bit of difficulty
- Some difficulty
- A little difficulty
- Hardly any difficulty
- No difficulty; the bowel problems did not limit sports or leisure activities

4. How often during the last 2 weeks have you been troubled by pain in the abdomen? Please choose an option from (Bowel)

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time

- Hardly any of the time
- None of the time

5. How often during the last 2 weeks have you felt depressed or discouraged? Please choose an option from (Emotional)
   - All of the time
   - Most of the time
   - A good bit of the time
   - Some of the time
   - A little of the time
   - Hardly any of the time
   - None of the time

6. Overall, in the last 2 weeks, how much of a problem have you had with passing large amounts of gas? Please choose an option from (Bowel)
   - A major problem
   - A big problem
   - A significant problem
   - Some trouble
   - A little trouble
   - Hardly any trouble
   - No trouble

7. Overall, in the last 2 weeks, how much of a problem have you had maintaining or getting to, the weight you would like to be at? Please choose an option from (Systemic)

- A major problem
- A big problem
- A significant problem
- Some trouble
- A little trouble
- Hardly any trouble
- No trouble

8. How often during the last 2 weeks have you felt relaxed and free of tension? Please choose an option form (Emotional)

- None of the time
- A little of the time
- Some of the time
- A good bit of the time
- Most of the time
- Almost all of the time
- All of the time

9. How much of the time during the last 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty? Please choose an option from (Bowel)

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time

- Hardly any of the time
- None of the time

10. How much of the time during the last 2 weeks have you felt angry as a result of your bowel problem? Please choose an option from (Emotional)

- All of the time
- Most of the time
- A good bit of the time
- Some of the time
- A little of the time
- Hardly any of the time
- None of the time

Appendix D. Health Care Resource Utilization (Unscheduled Outpatient Visits, Emergency Room Visits and Hospitalizations)

1. Since the last study visit has the subject had any physician/health care visits for their Crohn's disease other than the protocol visits?

☐ No ☐ Yes (if yes provide the following)

Type of Visit	2. Number of Visits	3. Total Number of Days
Physician		
Emergency Room		
Hospital Admission		

Appendix E. Work Productivity and Activity Impairment

The following questions ask about the effect of your Crohn's disease 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)? If NO, check "NO" and skip to question 6.	_____No	_____Yes
The next questions refer to 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 Crohn's disease? Include hours you missed on sick days, times you went in late, left early etc., because of your Crohn's disease. 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? If "0," write"0" and skip to question 6.	____ hours	
5) During the past seven days, how much did your Crohn's disease 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 Crohn's disease affected your work only a little, choose a low* number. Choose a high number if Crohn's disease affected your work a great deal.		
Crohn's Disease had no effect on my work 0 1 2 3 4 5 6 7 8 9 10 CIRCLE A NUMBER Crohn's Disease completely prevented me from doing my work		
6) During the past seven days, how much did your Crohn's disease 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 Crohn's disease affected your activities only a little, choose a low number. Choose a high number if Crohn's disease affected your activities a great deal.*		
Crohn's Disease had no effect on my daily activities 0 1 2 3 4 5 6 7 8 9 10 CIRCLE A NUMBER Crohn's Disease completely prevented me from doing my daily activities		

Appendix F. Physician's Global Assessment

Physician's Global Assessment*		
		Subscore
General Well Being (based on subject's recall of prior seven days)		
0 = Very well 1 = Slightly below par 2 = Poor	3 = Very poor 4 = Terrible	= _____
Abdominal Pain (based on subject's recall of prior seven days) 0 = None 1 = Mild 2 = Moderate 3 = Severe		= _____
Diarrhea (average total number of liquid or very liquid stools per 24 hours based on subject's recall of the prior seven days)		= _____
Blood in Stool (based on subject's recall of prior seven days) 0 = None 1 = Occasional 2 = Frequent		= _____
Abdominal mass 0 = None 1 = Dubious 2 = Definite 3 = Definite and tender		= _____
Complications (score 1 per item) Arthralgia/Arthritis Iritis/Uveitis Erythema nodosum	 Oral aphthous ulcers Anal fissure Draining fistula	= _____
Pyoderma gangrenosum	Abscess	
	Score (Sum of subscores)	= _____

* Derived from the Harvey Bradshaw scoring system for Crohn's Disease. Harvey RF, Bradshaw JM. A simple index of Crohn's-disease activity. Lancet 1980;1:514-514.

Appendix G. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

Specific Protocol Changes:

Global changes made throughout protocol

Changed: HUMIRA to Humira

Changed: eDRF to eCRF

Changed: DRF to CRF

Section 1.0 Title Page
"Emergency Contact:"
Previously read:

Emergency Contact:	[redacted] Global Medical Director Immunology Global Pharmaceutical Research and Development AbbVie Inc. 1 North Waukegan Road North Chicago, IL 60064	[redacted]

Has been changed to read:

Emergency Contact:	[redacted] Immunology Global Pharmaceutical Research and Development AbbVie Inc. 1 North Waukegan Road North Chicago, IL 60064	Phone: +1 847-935-2495 [redacted]

Section 1.0 Title Page
"CRO(s):"
Previously read:

CRO(s): [redacted]
Director, Global Projects
REGISTRAT-MAPI
2343 Alexandria Drive, Suite 400
Lexington, KY 40504-3276
[redacted]

Has been changed to read:

CRO: [redacted]
Global Program Director
REGISTRAT-MAPI
1235 Westlakes Blvd., Suite 100
Berwyn, PA 19312
[redacted]

Section 1.0 Title Page
Disclaimer previously read:

This study will be conducted in compliance with the protocol, Good Clinical Practice and all other applicable regulatory requirements, including the archiving of essential documents.

Has been changed to read:

This study will be conducted in compliance with the protocol and all other applicable regulatory requirements, including the archiving of essential documents.

Section 3.0 Introduction
Eleventh paragraph, fifth, sixth and seventh sentences
Previously read:

These case reports, and are derived from a variety of sources including registries and spontaneous post-marketing reports.[10] Rare post-marketing cases of hepatosplenic T-cell lymphoma, have been identified in patients treated with TNF-antagonists including adalimumab.[18,19] This rare type of T-cell lymphoma, has a very aggressive disease course and is usually fatal.

Has been changed to read:

These case reports are derived from a variety of sources including registries and spontaneous post-marketing reports.[10] Rare post-marketing cases of hepatosplenic T-cell lymphoma have been identified in patients treated with TNF-antagonists including adalimumab.[18,19] This rare type of T-cell lymphoma, has a very aggressive disease course and is usually fatal.[16]

Section 3.1 Safety Information
Add: new section and text

3.1 Safety Information

Adalimumab therapy has a well established and well described safety profile based on extensive postmarketing experience and continued clinical trial patient exposure since the first approved indication in 2002 for rheumatoid arthritis. A detailed discussion of the clinical toxicology, metabolism, pharmacology and safety experience with adalimumab can be found in the current Package Insert. AbbVie is committed to continue to collect safety information including those events that may occur in this trial in order to confirm the established safety profile and to identify unknown potential adverse reactions, rare events and those events with a long latency. AbbVie is participating in an FDA-requested, TNF-inhibitor class wide exploration of the rare appearance of malignancy in patients who are 30 years of age or younger at the time of diagnosis. The risk of malignancy in this age group has not been established and is difficult to study due to its rarity. AbbVie appreciates your attention to the additional reporting requirements needed in this unlikely event, as outlined in Section 7.5 under Adverse Event Reporting.

Section 4.0 Rationale
Second and fourth paragraphs
Previously read:

The sample size for the Registry is 5,000 patients. Based on more recent literature data regarding the expected rate for the adverse event of lymphoma that indicated a lower frequency than previously estimated and a discussion with the FDA, the registry duration

has been extended to 6 years and the follow-up procedures for patients who discontinue the registry have been added to the protocol to maximize the safety information collected from all registry patients.

The data collected in this Registry will be complementary to those from the pre-registration studies of adalimumab in CD. The management of the patients in this Registry reflects the current clinical practice. The participating Physician is free to determine the appropriate therapy for each patient and make treatment choices as deemed clinically necessary. All patients that consent to take part in the registry will be followed for up to 6 years, providing unique long-term safety and effectiveness data on HUMIRA in CD.

Has been changed to read:

The sample size for the Registry is 5,000 patients. Recent literature data describes a lower expected rate for the adverse event of lymphoma than previous estimates; therefore, following a discussion with the FDA, the registry duration has been extended to 6 years. In addition, follow-up procedures for patients who discontinue the registry have been added to the protocol to maximize the safety information which may be collected from all registry patients.

The data collected in this Registry will be complementary to those from the pre-registration studies of adalimumab in CD. The management of the patients in this Registry reflects the current clinical practice. The participating physician is free to determine the appropriate therapy for each patient and make treatment choices as deemed clinically necessary. All patients that consent to take part in the registry will be followed for up to 6 years, providing long-term safety and effectiveness data on Humira in CD.

Section 6.0 Investigational Plan
Following sixth paragraph, third paragraph
Add: fifth and sixth sentences

An HCP is not considered a participating investigator in the registry since they are only completing an annual questionnaire on behalf of a former registry patient. Participating registry investigators for which all of their patients have discontinued from registry participation may convert to an HCP status if their patients(s) choose to participate in the HCP process.

Section 6.2.1 Inclusion Criteria
Following Item 1, third bullet previously read:

- Patients who were prior participants in AbbVie sponsored investigational Crohn's disease trials, who have not had dose interruptions since the last dose of study drug, where the Investigator can provide source documentation of dosing information.

Hs been changed to read:

- Patients who were prior participants in AbbVie sponsored investigational Crohn's disease trials, who have not had dose interruptions since the last dose of registry drug, where the Investigator can provide source documentation of dosing information.

Table 1. Schedule of Study Assessments
Three Procedures, "All Concomitant Medications," "Concomitant CD Medications" and "Data Report Form Completion"
Previously read:

Procedure	Study Enrollment	Month[a] 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72	At Time of Reported Event
Concomitant CD Medications	√	√	√
All Concomitant Medications			√
Data Report Form Completion	√	√	√

Has been changed to read:

Procedure	Study Enrollment	Month[a] 3, 6, 9, 12, 18, 24, 30, 36, 42, 48, 54, 60, 66 and 72	At Time of Reported Event
Prior and Concomitant CD Medications	√	√	√
All Concomitant Medications	√		√
Case Report Form Completion	√	√	√

Section 6.4.5 Concomitant Medications
Title of section and text previously red:

6.4.5 Concomitant Medications

Any previous medications (corticosteroids, aminosalicylates, anti-TNF drugs including commercial HUMIRA, immunosuppressants [i.e., azathioprine, 6-mercaptopurine, methotrexate] and antibiotics) used to treat CD will be captured at the study enrollment visit. Information on the highest maintained dose, date of last administration, length of time on the medication and reason for stopping the CD medication will be collected in the source documents and appropriate eDRF pages.

All concomitant medications the subject is receiving at the Registry enrollment visit should be recorded in the source documents and on the appropriate page of the eDRF

along with the reason for use, duration of use and dosages. Information on medications taken for CD (including dose changes) and a complete list of all medications taken at the time of a serious adverse events or events of interest will be collected throughout the Registry.

For patients who are enrolled in the Registry, after the initiation of HUMIRA therapy, all concomitant medication changes from the initiation of HUMIRA therapy until enrollment into the Registry will need to be captured.

The administration of anakinra (Kineret®) or other biologic agents may not be given concurrently while on HUMIRA. Please refer to your local product label for information regarding the use of live vaccines while a patient is on HUMIRA.

AbbVie will not provide any medication or therapy for this Registry.

Has been changed to read:

6.4.5 Prior and Concomitant Medications

Any previous medications (corticosteroids, aminosalicylates, anti-TNF drugs including commercial Humira, immunosuppressants [i.e., azathioprine, 6-mercaptopurine, methotrexate] and antibiotics) used to treat CD will be captured at the study enrollment visit. Information on the highest maintained dose, date of last administration, length of time on the medication and reason for stopping the CD medication will be collected in the source documents and appropriate eCRF pages.

All concomitant medications the subject is receiving at the Registry enrollment visit should be recorded in the source documents and on the appropriate page of the eCRF along with the reason for use, duration of use and dosages. Information on medications taken for CD (including dose changes) and a complete list of all medications taken at the time of a serious adverse event or adverse events of interest will be collected throughout the Registry.

For patients who are enrolled in the Registry, after the initiation of Humira therapy, all concomitant medication changes from the initiation of Humira therapy until enrollment into the Registry will need to be captured.

In addition, for patients age ≤ 30 with a reported malignancy adverse event, prior exposure to, or current use of, antineoplastics, or other drugs which have a risk of malignancy as stated in their label and other relevant dosing information to estimate total exposure will be collected in the source documents and appropriate eCRF pages. At the time of the reported malignancy adverse event, sites will be asked if any of the prior and concomitant medications contributed to the event. Any medications used prior to the study will be captured on the appropriate eCRF. Information on the reason for use, date(s) of administration including start and end dates, highest maintained dose, dosage information including dose, route and frequency, and reason for stopping the medication will be collected in the source documents and appropriate eCRF pages.

The administration of anakinra (Kineret®) or other biologic agents may not be given concurrently while on Humira. Please refer to your local product label for information regarding the use of live vaccines while a patient is on Humira.

The Study Designated Physician identified in Section 7.5 should be contacted if there are any questions regarding prior or concomitant medications.

After registry enrollment, patients should not be enrolled into any interventional clinical trial.

AbbVie will not provide any medication or therapy for this Registry.

Section 6.4.8 Adalimumab Treatment and Dosing Changes
Third paragraph, third sentence previously read:

The site will fax completed forms into the designated Study Help Desk.

Has been changed to read:

The site will fax or email completed forms into the designated Study Help Desk.

Section 6.4.8 Adalimumab Treatment and Dosing Changes
Sixth paragraph previously read:

If a patient completes the 6-year observation period a Termination Data Report Form (eTDRF) should be completed.

Has been changed to read:

If a patient completes the 6-year observation period study completion eCRFs should be completed.

Section 6.5 Withdrawal of Patients from Registry
First paragraph, last sentence previously read:

If a patient completes the 6-year observation period a Termination Data Report Form (eTDRF) should be completed.

Has been changed to read:

If a patient withdraws or is lost to follow up, such should be noted, along with the reason for withdrawal on the study completion eCRF.

Section 7.0 Adverse Events/Adverse Event Reporting
Previously read:

The Physician will monitor each patient for serious adverse events and pre-defined adverse events of interest on a routine basis throughout the registry. The Physician will assess and record any serious adverse event and adverse event of interest in detail including the date of onset, description, severity, time course, duration and outcome (when known), relationship of the adverse event to drug, an event diagnosis, if known, and any action(s) taken. For events not considered "probably related" to study drug, the Physician will provide another cause of the event. Serious adverse events or adverse

events of interest, whether in response to a query, observed by site personnel, or reported spontaneously by the patient will be recorded. Information about any concomitant medications taken at the time of the SAE or the adverse events of interest will be collected. For all AEs of Special Interest, the physician must pursue and obtain all the above mentioned information in order to adequately determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE as well as to determine a causal relationship.

Has been changed to read:

The physician will monitor each patient for serious adverse events and adverse events of interest throughout the patient's participation in the registry or direct to HCP process, and/or until 70 days following discontinuation of Humira administration have elapsed (whichever period is longer). The physician will assess and record any serious adverse event and adverse events of interest in detail including the date of onset, description, severity, time course, duration and outcome (when known), relationship of the adverse event to drug, an event diagnosis, if known, and any action(s) taken. For SAEs not considered "probably related" to registry drug, the physician will provide another cause of the event. Serious adverse events or adverse events of interest, whether in response to a query, observed by site personnel, or reported spontaneously by the patient will be recorded. Information about any concomitant medications taken at the time of the SAE or the adverse events of interest will be collected. For all adverse events of interest, the physician must pursue and obtain all the above mentioned information in order to adequately determine the outcome of the AE and to assess whether it meets the criteria for classification as an SAE as well as to determine a causal relationship.

Section 7.1.1 Adverse Events
Add: third paragraph

An elective surgery/procedure scheduled to occur during the registry will not be considered an SAE if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure was planned prior to entry into the registry. However, if the pre-existing condition deteriorates unexpectedly during the registry

(e.g., surgery performed earlier than planned) then the deterioration of the condition for which the elective surgery/procedure is being done will be considered an adverse event.

Section 7.1.2 Adverse Events of Interest
First paragraph previously read:

The Physician will monitor each patient for clinical and laboratory evidence for pre-defined adverse events of interest at the Baseline visit and on a routine basis throughout the registry.

Has been changed to read:

The physician will monitor each patient for clinical and laboratory evidence for adverse events of interest at the Baseline visit and on a routine basis throughout the registry.

Section 7.1.2 Adverse Events of Interest
Third paragraph previously read:

During the course of the registry additional AEs of special interest may be identified by AbbVie. Updates to the AEs of special interest will be maintained and collected through the eDRF system. Sites will be trained on all updates to the eDRF system.

Has been changed to read:

During the course of the registry additional adverse events of interest may be identified by AbbVie. Updates to the adverse events of interest will be maintained and collected through the eCRF system. Sites will be trained on all updates to the eCRF system.

Section 7.3 Relationship to Pharmaceutical Products
Previously read:

Probably Related	An adverse event has a strong temporal relationship to study drug or recurs on re-challenge and another cause of event is unlikely or significantly less likely.
Possibly Related	An adverse event has a strong temporal relationship to the study drug and another cause of event is equally or less likely compared to the potential relationship to study drug.
Probably Not Related	An adverse event has little or no temporal relationship to the study drug and/or a more likely other cause of event exists.
Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the study drug (e.g., has no temporal relationship to study drug or has a much more likely other cause of event).

Has been changed to read:

Probably Related	An adverse event has a strong temporal relationship to registry drug or recurs on re-challenge and another cause of event is unlikely or significantly less likely.
Possibly Related	An adverse event has a strong temporal relationship to the registry drug and another cause of event is equally or less likely compared to the potential relationship to registry drug.
Probably Not Related	An adverse event has little or no temporal relationship to the registry drug and/or a more likely other cause of event exists.
Not Related	An adverse event is due to an underlying or concurrent illness or effect of another drug and is not related to the registry drug (e.g., has no temporal relationship to registry drug or has a much more likely other cause of event).

Section 7.4 Adverse Event Collection Period
Previously read:

Serious adverse events and adverse events of interest will be reported to Abbott from the time the physician obtains the subject's initial authorization to use and disclose information (or the subject's informed consent) throughout the patient's participation in the Registry, up to 6 years, and followed to a satisfactory clinical outcome. A medical event that occurs after a patient discontinues the registry that is considered to be related to

the patient's exposure to HUMIRA will be reported via standard post-marketing reporting practices.

In the event HUMIRA therapy is interrupted, SAEs and adverse events of interest will be collected throughout the interruption. If treatment with adalimumab is permanently discontinued for any reason, the reason will be recorded and the patients should be encouraged to remain in the registry for the full 6 years so important safety information can be obtained. For patients enrolled from a prior CD study, ongoing events at the time of Registry entry will be collected and resolved within the primary clinical trial.

Has been changed to read:

Serious adverse events and adverse events of interest will be reported to AbbVie from the time the physician obtains the subject's initial authorization to use and disclose information (or the subject's informed consent) throughout the patient's participation in the Registry, or direct to HCP process, and/or until 70 days following discontinuation of Humira administration have elapsed (whichever period is longer). A medical event that occurs after a patient discontinues the registry that is considered to be related to the patient's exposure to Humira will be reported via standard post-marketing reporting practices.

In the event Humira therapy is interrupted, SAEs and adverse events of interest will be collected throughout the interruption. If treatment with adalimumab is permanently discontinued for any reason, the reason will be recorded and the patients should be encouraged to remain in the registry for the full 6 years so important safety information can be obtained.

Section 7.5 Adverse Event Reporting
Previously read:

In the event of a serious adverse event, whether related to adalimumab or not, the physician will complete and submit the Serious Adverse Event (SAE) information into the

electronic data capture system (EDC) within 24 hours of being made aware of the serious adverse event.

If the EDC system is unavailable, the completed Serious Adverse Event Form should be submitted via fax or email to:

The completed Serious Adverse Event Form will be submitted via fax or email to:

Name	Phone	Email
AbbVie Clinical Safety Management	+1-847-775-6705	immunologysafety@abbvie.com

If you have a medical question in regards to a Serious Adverse Event, please contact the following persons:

AbbVie Safety & Medical Contact			
Name/Function	**Address**	**Phone/Fax**	**Email**
[redacted]	[redacted]	[redacted]	[redacted].com

Has been changed to read:

In the event of an SAE, and/or additionally, any nonserious event of malignancy in patients 30 years of age and younger, whether related to Humira or not, the physician will notify the AbbVie Immunology Clinical Safety Management Team within 24 hours of the physician becoming aware of the event by entering the serious adverse event and/or nonserious event of malignancy in patients 30 years of age and younger data into the electronic data capture (EDC) system.

Serious adverse events and nonserious events of malignancy in patients 30 years of age and younger, that occur prior to the site having access to the EDC system should be faxed to the AbbVie Immunology Clinical Safety Management Team within 24 hours of being made aware of the adverse event.

If the EDC system is unavailable, the completed Serious Adverse Event Form should be submitted via fax:

FAX to: +1 (847) 785-8227

For SAE concerns, contact the Immunology Safety Team at:

Immunology Safety Team
AbbVie
Dept. R477, Bldg. AP4-2
1 North Waukegan Road
North Chicago, IL 60064

Safety Hotline: +1 (847) 938-8737
Fax: +1 (847) 785-8227
Email: GPRD SafetyManagement Immunology@abbvie.com

For any subject safety concerns, please contact the physician listed below:

AbbVie Safety and Medical Contact			
Name/Function	**Address**	**Phone/Fax**	**Email**
[redacted]	[redacted]	[redacted]	[redacted]

Section 7.6 Pregnancy
Previously read:

Pregnancy must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. HUMIRA Physicians should refer to their local prescribing information when making treatment decisions for patients who become pregnant while being treated with HUMIRA in the Registry. Patients who become pregnant and interrupt their HUMIRA therapy should remain in the registry and should continue to be monitored for new SAE and AEs of Interest.

All female patients who become pregnant while enrolled in the registry will be followed from the time of pregnancy is reported until the outcome of the pregnancy is known. Information regarding a pregnancy occurrence in a registry patient and the outcome of the pregnancy will be collected. Upon notification of a pregnancy, AbbVie will forward a form to the site for the Investigator to complete and return it to AbbVie. A second form will be sent approximately 9 months from the date of notification to collect information on the outcome of the pregnancy. This form will also be completed and returned to AbbVie.

To monitor outcomes of pregnant women exposed to HUMIRA, a pregnancy registry has been established in the United States and Canada (http://www.otispregnancy.org/). Patients and physicians in the United States and Canada are encouraged to register patients by calling 1-877-311-8972 and/or provide this information to the subject.

Pregnancy in a registry patient is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

Has been changed to read:

Pregnancy in a registry patient must be reported to AbbVie within 1 working day of the site becoming aware of the pregnancy. Pregnancies will be collected from the date of the first dose through 150 days following the last dose of registry dose.

Physicians should refer to their local prescribing information when making treatment decisions for patients who become pregnant while being treated with Humira in the Registry. Patients who become pregnant and interrupt their Humira therapy should remain in the registry and should continue to be monitored for new SAEs and adverse events of Interest.

All female patients who become pregnant while enrolled in the registry will be followed from the time of pregnancy is reported until the outcome of the pregnancy is known.

Information regarding a pregnancy occurrence in a registry patient and the outcome of the pregnancy will be collected.

Pregnancy in a registry patient is not considered an adverse event. However, the medical outcome of an elective or spontaneous abortion, stillbirth, or congenital anomaly is considered a serious adverse event and must be reported to AbbVie within 24 hours of the site becoming aware of the event.

Section 7.7 Data Collection Procedures for Patients who Re-enroll in the Registry
Section title and text previously read:

7.7 Data Collection Procedures for Patients who Re-enroll in the Registry

For patients who re-enroll in the registry, registry physicians will document any hospitalizations or surgeries and any adverse event of interests as defined in Section 7.1.2 via a paper questionnaire. The physician will assess and record the date of onset (where known) and description of the event. The use of other medications used to treat CD, and the stop and the restart dates for HUMIRA will be collected on an annual basis.

These events will be reported on the paper CRF to AbbVie from the time of initial registry discontinuation through the date of re-enrollment, irrespective of any treatment interruption, any changes in treatment, or discontinuation of adalimumab.

Effectiveness data will not be collected during the timeframe when the patient was not participating in the registry.

For visits occurring after re-enrollment, registry physicians will resume data collection in the eDRF process as outlined in the protocol. The duration of follow-up includes the time from initial registry consent up to 6 years.

Has been changed to read:

7.7 Data Collection Procedures for Patients Who Re-enroll in the Registry

For patients who re-enroll in the registry, registry physicians will document any hospitalizations, surgeries, and any adverse event of interests as defined in Section 7.1.2. The physician will assess and record the date of onset (where known) and description of the event. These events will be reported via eCRF from the time of initial registry discontinuation through the date of re-enrollment, irrespective of any treatment interruption, any changes in treatment, or discontinuation of adalimumab.

The use of other medications used to treat CD and the stop and the restart dates for Humira, as applicable, from the time of initial registry discontinuation through the date of re-enrollment will be collected.

Effectiveness data will not be collected during the timeframe when the patient was not participating in the registry.

For visits occurring after re-enrollment, registry physicians will resume data collection in the eCRF process as outlined in the protocol. The duration of follow-up includes the time from initial registry consent up to 6 years.

Section 7.8 Data Collection Procedures for Patients Who Participate in the Direct to HCP Process
First paragraph, first sentence previously read:

For patients participating in the direct to HCP process, HCPs will document any hospitalizations or surgeries and any adverse event of interest as defined in Section 7.1.2 annually via a paper questionnaire.

Has been changed to read:

For patients participating in the direct to HCP process, HCPs will document any hospitalizations or surgeries and any adverse event of interest as defined in Section 7.1.2 annually via a paper questionnaire or EDC.

Section 8.2 Quality Assurance
Second paragraph, first sentence
Previously read:

Ten percent (10%) of the registry sites will be monitored on-site for the study.

Has been changed to read:

Approximately ten percent (10%) of the registry sites will be monitored on-site for the study.

Section 9.2 Case Report Forms
Fifth paragraph previously read:

Upon completion of or termination from the registry, all patients should have a Termination Data Report Form (eTDRF) completed as well as an assessment of their current medical conditions.

Has been changed to read:

Upon completion of or termination from the registry, all patients should have study completion eCRFs completed as well as an assessment of their current medical conditions.

Section 10.5 Safety Analyses
First paragraph previously read:

For the Registry Safety Population, treatment-emergent SAEs and AEs of interest will be summarized. Treatment-emergent SAEs and AEs of interest are defined as: (1) new events that begin either on or after the first dose of HUMIRA through the last dose of HUMIRA plus 70 days; or (2) increase in severity of ongoing SAEs that had occurred

before the first dose date of HUMIRA. The number and percent of patients experiencing SAEs and AEs of interest will be tabulated by body system and Medical Dictionary for Drug Regulatory Activities (MedDRA®) preferred term. The percent of patients will be presented with 95% confidence intervals. In addition, summary of SAEs and AEs of interest by severity and relationship to study drug will be presented.

Has been changed to read:

For the Registry Safety Population, treatment-emergent SAEs and adverse events of interest will be summarized. Treatment-emergent SAEs and adverse events of interest are defined as: (1) new events that begin either on or after the first dose of Humira through the last dose of Humira plus 70 days; or (2) increase in severity of ongoing SAEs that had occurred before the first dose date of Humira. The number and percent of patients experiencing SAEs and adverse events of interest will be tabulated by body system and Medical Dictionary for Drug Regulatory Activities (MedDRA®) preferred term. The percent of patients will be presented with 95% confidence intervals. In addition, summary of SAEs and adverse events of interest by severity and relationship to registry drug will be presented.

Section 12.0 Completion of the Registry
Add: last sentence

The end-of-registry is defined as the date of the patient's last visit in the registry or the HCP process, whichever occurs later.

Appendix A. List of Abbreviations and Definition of Terms
"DCRF," "eDRF," "eow"
Previously read:

DRF	Data Report Form
eDRF	Electronic Data Report Form
eow	Every Other Week

Has been changed to read:

CRF	Case Report Form
eCRF	Electronic Case Report Form
EOW	Every Other Week

Appendix A. List of Abbreviations and Definition of Terms
Add: new abbreviation

HCP	Health Care Provider

Appendix B. List of Protocol Signatories
Previously read:

Name	Title	Functional Area
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Has been changed to read:

Name	Title	Functional Area
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

Document Approval

Study P06134 - A Long-Term Non-Interventional Registry to Assess Safety and Effectiveness of HUMIRA (Adalimumab) in Subjects with Moderately to Severely Active Crohn's Disease (CD) - Amendment 3 - 18Jun2013

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Signed by:	Date:	Meaning Of Signature:
[redacted]	**18-Jun-2013 02:11:29 PM**	**Approver**
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[redacted]	**18-Jun-2013 06:24:59 PM**	**Approver**
[redacted]	**18-Jun-2013 07:49:26 PM**	**Approver**
[redacted]	**19-Jun-2013 01:09:44 PM**	**Approver**