


## Title Page

<b>Title</b>	An ObserVational STudy of the Effectiveness of <b>AdaLimumab</b> on Health and Disability Outcomes in New Zealand Patients with Immune-Mediated Inflammato <b>rY</b> Diseases ( <b>VITALITY</b> )
<b>Protocol Version Identifier</b>	P15-345
<b>Date of Last Version of Protocol</b>	21 April 2015
<b>EU PAS Register Number</b>	Not registered
<b>Marketing Authorisation Holder(s)</b>	AbbVie Limited
<b>Research Question and Objectives</b>	The objective of this study is to assess the effect of adalimumab on health and disability outcomes in patients with the immune-mediated inflammatory diseases of rheumatoid arthritis, Crohn's disease and psoriasis.
<b>Country of Study</b>	New Zealand
<b>Author</b>	

**This study will be conducted in compliance with this protocol.**

### **Confidential Information**

**No use or disclosure outside AbbVie is permitted without prior written authorization from AbbVie.**

## Marketing Authorisation Holder(s)

<b>Marketing Authorisation Holder(s)</b>	AbbVie Limited L6, 156–158 Victoria Street Wellington PO Box 11437, Manners Street Wellington NEW ZEALAND
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## 2.0 Abbreviations

<b>CDAI</b>	Crohn's Disease Activity Index
<b>CRF</b>	Case Report Form
<b>CRP</b>	C-Reactive Protein
<b>DLQI</b>	Dermatology Life Quality Index
<b>EU</b>	European Union
<b>FPFV</b>	First Patient First Visit
<b>FPLV</b>	First Patient Last Visit
<b>GCP</b>	Good Clinical Practice
<b>HAQ-DI</b>	Health Assessment Questionnaire–Disability Index
<b>ICH</b>	International Conference on Harmonization
<b>IEC</b>	Independent Ethics Committee
<b>IMID</b>	Immune-Mediated Inflammatory Diseases
<b>IRB</b>	Independent Review Board
<b>K10</b>	Kessler Psychological Distress Scale
<b>LPFV</b>	Last Patient First Visit
<b>LPLV</b>	Last Patient Last Visit
<b>PASI</b>	Psoriasis Area and Severity Index
<b>PDF</b>	Portable Document Format
<b>PP</b>	Per Protocol
<b>PPD</b>	Purified Protein Derivative
<b>PRO</b>	Patient-Reported Outcomes
<b>QoL</b>	Quality of Life
<b>RA</b>	Rheumatoid Arthritis
<b>RAP</b>	Reporting and Analysis Plan
<b>SAE</b>	Serious Adverse Event
<b>SAP</b>	Statistical Analysis Plan
<b>SD</b>	Standard Deviation
<b>SIBDQ</b>	Short Inflammatory Bowel Disease Questionnaire
<b>SOP</b>	Standard Operating Procedure
<b>TNF</b>	Tumour Necrosis Factor
<b>WHODAS 2.0</b>	The World Health Organisation Disability Assessment Schedule 2.0
<b>WPAI:GH</b>	The Work Productivity and Activity Impairment Questionnaire: General Health V2.0

### 3.0 Responsible Parties

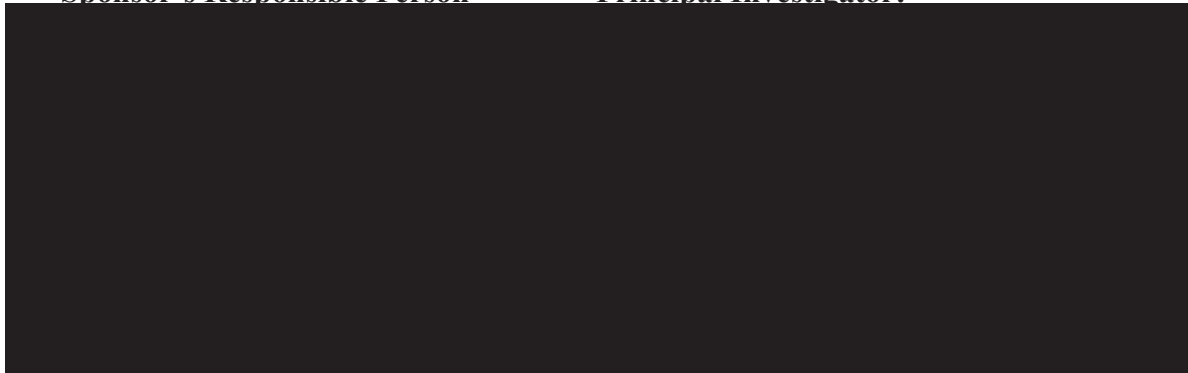
**Sponsor**

AbbVie Limited  
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PO Box 11437, Manners Street  
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New Zealand



**Sponsor's Responsible Person**

**Principal Investigator:**



**Clinical Project Manager**

**Monitoring CRO**



**Study-Designated Physician**



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## PROTOCOL SIGNATURES

### **Investigator Signature:**

I have read and agree to the Protocol Number P15-345, “An Observational Study of the Effectiveness of Adalimumab on Health and Disability Outcomes in New Zealand Patients with Immune-Mediated Inflammatory Diseases”. I am aware of my responsibilities as an investigator under the guidelines of Good Clinical Practices, local laws and regulations (as applicable) and the study protocol. I agree to conduct the study according to these laws and guidelines and to appropriately direct and assist the staff under my control, who will be involved in the study.

### **Principal (Site) Investigator:**

Name (typed or printed): \_\_\_\_\_

Institution and Address: \_\_\_\_\_

\_\_\_\_\_

\_\_\_\_\_

Telephone Number: \_\_\_\_\_

Signature: \_\_\_\_\_ Date: \_\_\_\_\_

(Day/ Month /Year)

Full investigational site contact details, including telephone numbers, will be documented in the Study Master File.



## 4.0 Abstract

**Title:** An Observational Study of the Effectiveness of Adalimumab on Health and Disability Outcomes in New Zealand Patients with Immune-Mediated Inflammatory Diseases (VITALITY)

**Rationale and Background:** For public health purposes disability is becoming increasingly important as an outcome measure. Despite this, there are few data on the effectiveness of adalimumab on disability outcomes in patients with Immune-Mediated Inflammatory Diseases (IMIDs), particularly in the Phase IV setting. There are even less data available in New Zealand, which did not have the opportunity to participate to a major extent in large, multinational, Phase III pivotal studies of adalimumab in IMIDs.

The World Health Organisation Disability Assessment Schedule (WHODAS) 2.0 is a simple, validated, free and easy-to-use generic assessment instrument for health and disability. It is applicable across cultures, in all adult populations. It is a responsive measure that can show what difference a treatment makes.

Results from study of effect of adalimumab on WHODAS scores and other Patient-Reported Outcomes (PRO) of work activity and well-being will be of interest to a variety of stakeholders in the healthcare system including patients, healthcare practitioners and payers.

**Research Question and Objectives:** The objective of this study is to assess the effect of adalimumab on health and disability outcomes in patients with the immune-mediated inflammatory diseases of rheumatoid arthritis, Crohn's disease and psoriasis.

**Study Design:** This is a Phase IV, parallel-group, observational, multicentre study designed to investigate the effectiveness of adalimumab on health and disability outcomes in New Zealand patients diagnosed with, rheumatoid arthritis, Crohn's disease and psoriasis.

Overall, a minimum of approximately 190 subjects with IMIDs are planned to be enrolled in the study at up to 15 sites. Approximately 80 subjects will be enrolled into each of 2 parallel study groups of patients diagnosed with rheumatoid arthritis or Crohn's disease. A minimum of 30 subjects with psoriasis will also be enrolled. All subjects will receive at least 3 months of treatment with adalimumab. Continuation of adalimumab will depend upon the patient meeting "Special Authority" response criteria between 3 and 6 months, which will allow continuing reimbursement of drug supply.

To assess health and disability outcomes, the WHODAS 2.0 score will be assessed at baseline, 2, 4 and 6 months after treatment initiation with adalimumab. In addition, other PROs of work activity and well-being, including the Work Productivity and Activity Impairment Questionnaire: General Health (WPAI:GH) V2.0, Kessler

Psychological Distress Scale (K10), Flourishing Scale, Subject Vitality Scale will also be administered at these time points. Disease-specific PROs that are commonly used in clinical practice (Health Assessment Questionnaire–Disability Index [HAQ-DI], Short Inflammatory Bowel Disease Questionnaire [SIBDQ], Dermatology Life Quality Index [DLQI]), will also be assessed. Variations of these disease-specific indices were used in some of the pivotal Phase III studies for adalimumab.

**Population:** Subjects will be males and/or females who are attending a routine clinical visit and meet all of the inclusion criteria and none of the exclusion criteria.

**Inclusion Criteria:**

1. Male and female
2. 18 to 75 years of age, inclusive.
3. Patients with a diagnosis of rheumatoid arthritis, Crohn’s disease or psoriasis who have made a decision with their physician to commence treatment with adalimumab in accordance with routine medical practice and with the approved adalimumab New Zealand datasheet.
4. Patients who have been evaluated for tuberculosis risk factors/exposure for active/latent tuberculosis infection (per local requirements and according to the approved adalimumab New Zealand Datasheet).
5. Subject has voluntarily signed and dated an informed consent form prior to any study-specific procedures.

**Exclusion Criteria:**

1. Previous treatment with adalimumab
2. Previous treatment with any biologic
3. Severe infection including sepsis, active tuberculosis or opportunistic infection.
4. Moderate to severe heart failure (New York Heart Association Class II/III)
5. Concurrent administration with anakinra
6. Hypersensitivity to adalimumab or its excipients
7. Any condition that in the opinion of the investigator would compromise the subject’s well-being or ability to perform the study requirements.

**Variables:** The primary outcome variable is change in WHODAS 2.0 response score at 6 months compared to baseline. Secondary outcome variables include WHODAS 2.0 response score at 2 and 4 months compared to baseline and other PRO measures of work activity and well-being, outlined above, at all study time points compared to baseline.

**Data Sources:** Case Report Forms (CRFs). Collection of data includes but not limited to subject demographics, adverse events, serious adverse events and concomitant medications. The following questionnaires will be utilized to collect data directly from participating subjects:

- WHODAS 2.0
- WPAI:GH V2.0
- K10
- Flourishing Scale
- Subject Vitality Scale
- Disease-specific PROs that are commonly used in clinical practice (HAQ-DI, SIBDQ, DLQI)

**Study Size:** It is anticipated that the three groups will respond differently to adalimumab treatment over the study period and there is reason to believe that these groups will be different at baseline. Therefore, the sample size will be powered for rheumatoid arthritis and Crohn's disease. Approximately 80 subjects will be enrolled into each of these 2 parallel study groups allowing for detection of within participant effect sizes of approximately 0.40 as statistically significant (2-tailed  $\alpha=0.05$ ) with 90% power. A minimum of 30 subjects with psoriasis will also be enrolled. A minimum number of 190 patients will be enrolled into the study.

**Data Analysis: Primary Endpoint Analysis**

Change in total WHODAS 2.0 score at 6 months after the initiation of adalimumab, in those patients continuing on adalimumab (responder population), across all indications. This change will be summarised as the mean and 95% confidence interval and will be tested with a paired t-test.

**Secondary Endpoint Analyses**

- Change in disease-specific indices (HAQ-DI, SIBDQ, DLQI), WPAI:GH, K10, Flourishing Scale, Subject Vitality Scale at 2, 4 and 6 months after the initiation of adalimumab, in those patients continuing on adalimumab (responder population). These changes will be summarised as the means and 95% confidence intervals and will be tested with paired t-tests.
- Change in total WHODAS 2.0 score at 6 months after the initiation of adalimumab, in those patients continuing on adalimumab (responder population), compared with those patients not continuing on adalimumab (non-responders). The mean changes in these two groups will be compared using an independent t-test.

## 5.0 Amendments and Updates

Number	Date	Section of Study Protocol	Amendment or Update	Reason
1	16SEP2015	<ul style="list-style-type: none"> <li>Title Page</li> <li>Milestones</li> <li>Study Design</li> <li>Setting</li> <li>Management and Reporting of Adverse Events</li> </ul>	<ul style="list-style-type: none"> <li>Addition of acronym to study title</li> <li>Update milestones based on FSFD</li> <li>Addition of guidance on discontinuation of individual subjects</li> <li>Addition of requirement around TB screening to inclusion criteria</li> <li>Clarification to Schedule of Events</li> <li>Addition of requirement around reporting of non-serious adverse events of malignancy in patients <math>\leq 30</math> years of age</li> </ul>	<ul style="list-style-type: none"> <li>Increase physician recall of study</li> <li>Updated timelines</li> <li>Process has been unclear</li> <li>Observational study – Requirement for TB screening should follow local requirements and according to the approved adalimumab New Zealand Datasheet</li> <li>Clarification of what is required at Baseline and timing of questionnaires</li> <li>Global Regulatory requirement</li> </ul>

A detailed summary of the changes is included in Annex 2.

## **6.0 Milestones**

Major study milestones and their planned dates are as follows:

Start of Data Collection (FPFV):	06 July 2015
End of Data Collection:	06 September 2016
Database Lock:	20 September 2016
Interim Database Lock:	01 March 2016
Interim Report:	31 March 2016
Final Report of Study Results:	11 November 2016

## **7.0 Rationale and Background**

Disability has been defined as impairments, activity limitations and participation restrictions due to personal and environmental factors (1). The concept of disability is one where a physical health condition or disease is evaluated in terms of its impact, difficulties, or limitations on a range of tasks, activities, or roles that are considered typical of everyday life. Examples of affected activities include basic aspects of daily living such as eating, bathing, dressing, household chores and meal preparation, or participation in society, or participation in work.

Along with traditional indicators of a population's health status, such as mortality and morbidity rates, disability has become increasingly important in measuring disease burden. Measuring disease activity and health-related quality of life (HRQOL) has become standard in many outcome studies, yet measures of disability are less commonly used. A complex interaction exists between all three of these elements.

The number of people with disabilities is growing (2). This is because populations are ageing – older people have a higher risk of disability – and because of the global increase in chronic health conditions associated with disability, such as the Immune-Mediated Inflammatory Diseases (IMIDs) of Crohn's disease, rheumatoid arthritis, and psoriasis.

Uncontrolled active rheumatoid arthritis causes joint damage, disability, decreased quality of life, and cardiovascular and other comorbidities (3). Likewise, patients with active Crohn's disease may experience repeat hospital admissions, multiple operations, poor nutrition, and malignancy, which can have a major impact on patients' education, work, and social and family life (4). Psoriasis is characterized by a combination of inflammation

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and epidermal thickening, resulting in thick, scaly skin patches, leading to a significant impairment of quality of life and profound psychosocial disability (5).

Adalimumab is a recombinant human immunoglobulin (IgG1) monoclonal antibody exclusively containing human peptide sequences. Adalimumab binds to tumour necrosis factor (TNF) and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. TNF is a naturally occurring cytokine that is involved in normal inflammatory and immune responses. Elevated levels of TNF are found in the synovial fluid of rheumatoid arthritis, including juvenile idiopathic arthritis, psoriatic arthritis and ankylosing spondylitis patients and play an important role in both the pathologic inflammation and the joint destruction that are hallmarks of these diseases. Increased levels of TNF are also found in psoriasis plaques, which contribute to the inflammatory response, to the proliferation and decreased maturation of keratinocytes and to the associated vascular damages that are characteristic of the disease (6).

Adalimumab has multiple registered indications in New Zealand across the therapeutic areas of rheumatology, gastroenterology and dermatology (rheumatoid arthritis, polyarticular juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, ulcerative colitis and psoriasis) and is subsidized by the New Zealand Government in some of these conditions, according to "Special Authority" criteria, which relate to disease severity. Registration and approval for subsidy were based on the results of a number of large, multinational, Phase III pivotal studies of adalimumab in IMIDs. The primary outcomes in these studies were effects of treatment on disease activity and health-related quality of life.

The World Health Organization Disability Assessment Schedule (WHODAS) 2.0 is a simple, validated, free- and easy-to-use generic assessment instrument for health and disability. It is applicable across cultures, in all adult populations. It is a responsive measure that can show what difference treatment makes (7).

The objective of this study is to assess the effect of adalimumab on health and disability outcomes in New Zealand patients with the IMIDs of rheumatoid arthritis, Crohn's disease and psoriasis. Results from study of the effect of adalimumab on WHODAS and other measures of work activity and well-being will be of interest to a variety of stakeholders in the healthcare system including patients, healthcare practitioners and payers in New Zealand.

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## **8.0 Research Question and Objectives**

The objective of this study is to assess the effect of adalimumab on health and disability outcomes in patients with the immune-mediated inflammatory diseases of rheumatoid arthritis, Crohn's disease, and psoriasis. The effect of adalimumab on health and disability outcomes in these patients will be assessed by the primary outcome measure which is the change in total WHODAS 2.0 (7) score at 6 months after the initiation of adalimumab, across all indications. It will also be assessed by the secondary outcome measures which are changes to the WPAI:GH V2.0 score (8), K10 score (9), Flourishing Scale (10) and Subject Vitality Scale (11) score at 6 months after the initiation of adalimumab, across all indications.

### **8.1 Hypothesis**

Adalimumab treatment will improve disability in subjects with rheumatoid arthritis, Crohn's disease, and psoriasis.

## **9.0 Research Methods**

### **9.1 Study Design**

This is a Phase IV, parallel-group, observational, multicentre study designed to investigate the effectiveness of adalimumab on health and disability outcomes in New Zealand patients diagnosed with rheumatoid arthritis, Crohn's disease and psoriasis.

The decision to commence treatment with adalimumab is to be made by the patient and the physician before including the patient in this study and has to be clearly separated and independent of the decision to include the patient in the study.

Overall, a minimum of approximately 190 subjects with these three IMIDs are planned to be enrolled in the study at up to 15 sites. Approximately 80 subjects will be enrolled into each of 2 parallel study groups of patients diagnosed with rheumatoid arthritis or Crohn's disease. A minimum of 30 subjects with psoriasis will also be enrolled. All subjects will receive at least 3 months of treatment with adalimumab. AbbVie is not supplying adalimumab; adalimumab is to be used according to the approved adalimumab New Zealand Datasheet and is to be prescribed by the physician under usual and customary practice of physician prescription. Continuation of adalimumab will depend upon the patient meeting the disease-specific response criteria as determined by the investigator



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between 3 and 6 months, which will allow continuing reimbursement of drug supply under “Special Authority”.

To assess health and disability outcomes, the WHODAS 2.0 score will be assessed at baseline, 2, 4 and 6 months after treatment initiation with adalimumab. Work productivity will be assessed at these time points using the WPAI:GH V2.0 (8). Psychological distress will be measured using the K10 scale (9). Subject happiness will also be measured, Flourishing Scale (10), Subject Vitality Scale (11). Disease-specific patient reported outcomes (PROs) that are more commonly used in clinical practice; Health Assessment Questionnaire–Disability Index (HAQ-DI) (12), Short Inflammatory Bowel Disease Questionnaire (SIBDQ) (13), Dermatology Life Quality Index (DLQI) (14) will also be assessed. Variations of these disease-specific indices were used in some of the pivotal Phase III studies for adalimumab.

As this is a non-interventional, observational study, no restrictions on dose modification or concomitant medications will be imposed at any time throughout the course of the study. Administration of adalimumab and follow up visits will be carried out according to investigators’ normal practice.

### **Primary Endpoint**

Change in total WHODAS 2.0 score at 6 months after the initiation of adalimumab, across all indications.

### **Secondary Endpoints**

- Change in total WHODAS score 2 and 4 months after the initiation of adalimumab across all indications
- Change in total WHODAS score 6 months after the initiation of adalimumab in each indication
- Changes in WPAI:GH V2.0 Scores, K10 scale, Flourishing Scale, Subject Vitality Scale at 6 months after the initiation of adalimumab, across all indications
- Change in disease-specific scores (HAQ-DI, SIBDQ, DLQI) at 6 months after the initiation of adalimumab, in each indication
- Proportion of patients at 6 months who remain on adalimumab, having satisfied the requirements for application for renewal of subsidy by “Special Authority”:
  - Rheumatoid arthritis:  $\geq 50\%$  decrease in active joint count from baseline AND a clinically significant response to treatment in the opinion of the physician
  - Crohn’s disease: Crohn's Disease Activity Index (CDAI) score reduction by 100 points or CDAI score  $\leq 150$



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- Psoriasis: Psoriasis Area and Severity Index (PASI) score reduction of  $\geq 75\%$ ; or in the case of a patient had severe chronic plaque psoriasis of the face, or palm of a hand or sole of a foot at the start of treatment, the patient has a reduction in the PASI symptom subscores for all 3 of erythema, thickness and scaling, to slight or better, OR  $\geq 75\%$  reduction in affected skin area.

No restriction on current standard of care is imposed. Physicians should treat their patients as they would in their routine clinical practice. Prior medical history, the use of any concomitant medication and any and all adverse events will be captured and recorded in the CRF.

As all procedures will be conducted in accordance with routine medical practice, participation in the study does not convey any additional risks for the subject. However, the subject will be provided with information on the benefits and risks of their medical treatment by the physician, in accordance with their routine medical practice.

Prior to collecting any study related information, written informed consent must be obtained.

Each subject has the right to withdraw from the study at any time. In addition, the investigator may discontinue a subject from the study at any time if the investigator considers it necessary for any reason, including the occurrence of an adverse event or noncompliance with the protocol.

In the event that a subject withdraws or is discontinued from the study, the primary reason for discontinuation and any other reason(s) for the discontinuation from the study will be recorded. If the reason for treatment discontinuation is due to a serious adverse event, it should be reported to AbbVie within 24 hours of physician's awareness.

Subjects will be withdrawn from the study immediately if any of the following occur:

- The investigator believes it is in the best interest of the subject.
- The subject or subject's guardian requests withdrawal from the study.
- A selection criteria violation was noted after the subject started adalimumab.

The study procedures to be conducted (if part of routine clinical practice) are outlined in the schematic presented in Table 1

## 9.1.1 Schedule of Events

**Table 1. Study Activities- Clinic Visits (Day 1/Baseline Through 6 months)**

Activity	Baseline (Day 1) <sup>a</sup>	Any time point between 3-6 months
Inclusion/Exclusion Criteria	X	
Informed Consent	X	
Demographics†		
Medical History*	X	
TB History Assessment <sup>b</sup>	X	
Concomitant Medications, Including Changes to	X	X
CRP (if available) <sup>c</sup>	X	X
Physician's Assessment of Disease Activity: Active joint count, or CDAI, or PASI	X	X
Adverse Events <sup>d</sup>	X	X

† Once the physician has determined that the patient is eligible for inclusion, and the patient has agreed to be included in the observational study, the patient's demographic data (including year of birth, gender, ethnicity) will be recorded on the CRFs at the Baseline visit

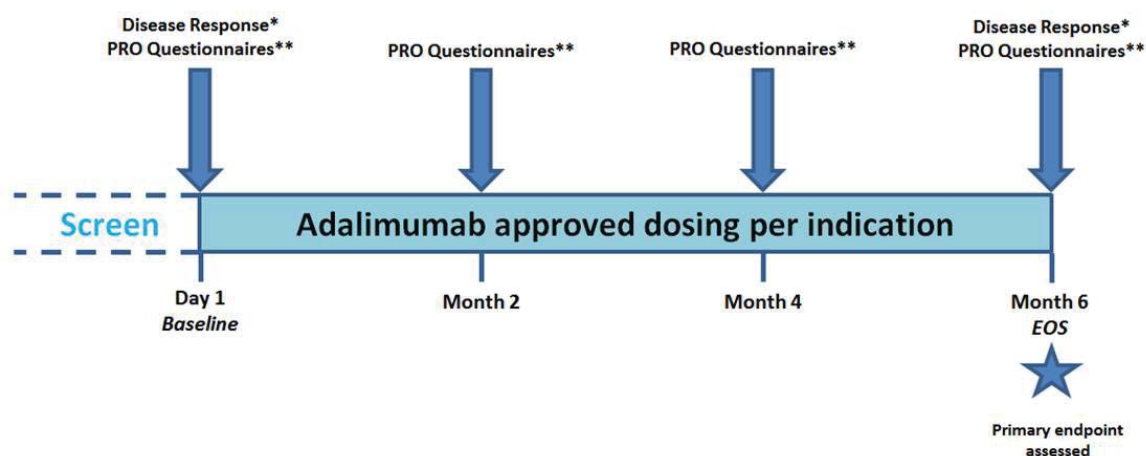
\*The physician will determine the patient's current health status and obtain a complete medical history including history of tobacco, date of diagnosis, disease activity, concomitant medications and TB exposure/risk factors at the Baseline visit.

**Table 2. Study Activities- Patient Activities (Day 1/Baseline Through 6 months)**

Activity	Baseline (Day 1) <sup>a</sup>	2 months	4 months	6 months
WHODAS 2.0 12-item version, self-administered	X	X	X	X
Disease-specific patient reported outcomes: HAQ-DI or SIBDQ or DLQI	X	X	X	X
Kessler Psychological Distress Scale (K10)	X	X	X	X
Work Productivity and Activity Impairment Questionnaire	X	X	X	X
Flourishing Scale	X	X	X	X
Subject Vitality Scale	X	X	X	X

- The Baseline visit date will serve as the reference for all subsequent visits. A  $\pm$  7 day window is permitted around scheduled study visits, however at Baseline patient questionnaires must be completed prior to the first dose of adalimumab.
- An assessment of TB exposure/risk factors for active and latent TB (per local requirements and according to the approved adalimumab NZ Datasheet) must have been completed prior to the first dose of adalimumab with documented history of results
- CRP will only be collected if procedure is performed as part of the usual standard of care
- Collection of adverse events begins the day the Subject signs the informed consent

Figure of study design:



\*Disease-specific measure of response to treatment:

- Active joint count, or CDAI, or PASI

\*\*PRO questionnaires (all self-administered):

- WHODAS 2.0 12-item version
- WPAI:GH V2.0
- K10
- Flourishing Scale
- Subject Vitality Scale
- Disease-specific outcomes: HAQ-DI or SIBDQ or DLQI

### 9.1.2 Physician's assessment of disease activity: Active joint count, or CDAI, or PASI

An assessment of disease activity by the Physician will be recorded at the Baseline Visit and within 3–6 months of initiation, as per standard of care.

### 9.1.3 PRO Questionnaires

Patients will complete the following questionnaires at the visits identified on the Study Activities Table (Table 1).

- 
- WHODAS 2.0
  - WPAI:GH V2.0
  - K10
  - Flourishing Scale
  - Subject Vitality Scale
  - A Disease-Specific patient reported outcome questionnaire:
    - HAQ-DI for patients with rheumatoid arthritis
    - SIBDQ for patients with Crohn's disease
    - DLQI for patients with psoriasis

At the Baseline visit, the questionnaires must be completed before the first dose of adalimumab.

#### **9.1.4 Adalimumab dosing**

The participating Physician will provide the patient with a prescription for adalimumab, along with instructions for appropriate use. The date of first dose of adalimumab will be recorded in the CRF and should closely align with the Baseline visit, but not before completion of the PRO questionnaires.

#### **9.1.5 Product Supply**

Adalimumab will be obtained as commercially available medication. AbbVie will not provide the medication for this study.

### **9.2 Setting**

The study will take place in New Zealand with multiple centres across the country. The study population shall comprise of male and/or female patients who are attending a routine clinical visit and meet all of the inclusion criteria and none of the exclusion criteria. Overall, a minimum of approximately 190 subjects with the three IMIDs are planned to be enrolled in the study at up to 15 sites.

As part of the inclusion criteria, the subjects will come from three clinically diagnosed areas:

- rheumatoid arthritis (80 patients)
- Crohn's disease (80 patients)
- psoriasis (30 patients)

The approved indications for the use of adalimumab in New Zealand for treatment of these conditions are as follows:

### **Rheumatoid Arthritis**

Humira is indicated for reducing signs and symptoms, as well as inhibiting the progression of structural damage in adult patients with moderate to severely active rheumatoid arthritis. This includes the treatment of patients with recently diagnosed moderate to severely active disease who have not received methotrexate.

Humira can be used alone or in combination with methotrexate.

### **Crohn's Disease in Adults and Children (≥6 years)**

Humira is indicated for the treatment of moderate to severe Crohn's disease to reduce the signs and symptoms of the disease and to induce and maintain clinical remission in patients;

- who have had an inadequate response to conventional therapies, or,
- who have lost response to or are intolerant of infliximab.

### **Psoriasis**

Humira is indicated for the treatment of moderate to severe chronic plaque psoriasis in adult patients who are candidates for systemic therapy or phototherapy.

AbbVie is not supplying adalimumab; adalimumab is to be used according to the approved adalimumab New Zealand Datasheet and is to be prescribed by the physician under usual and customary practice of physician prescription. To be eligible to receive New Zealand Government-subsidised access to adalimumab for these conditions, patients must meet certain "Special Authority" criteria, as defined by the Pharmaceutical Management Agency (PHARMAC). These criteria for initiation of adalimumab therapy are detailed in the inclusion/exclusion criteria. For continuation of subsidised access to adalimumab documentation of response to treatment must also be made.

It is the Investigator's responsibility to ensure that all inclusion/exclusion criteria are met. Subject selection may be completed by use of a relevant record (e.g. checklist of inclusion/exclusion criteria). Site personnel should thoroughly assess the eligibility criteria and evidence of this should be stored with the source documentation at site.

Where there is any deviation from the inclusion/exclusion criteria, the patient should be excluded from the study.

### **9.2.1 Inclusion Criteria:**

1. Male and female
2. 18 to 75 years of age, inclusive.
3. Patients with a diagnosis of rheumatoid arthritis, Crohn's disease or psoriasis who have made a decision with their physician to commence treatment with adalimumab in accordance with routine medical practice and with the approved adalimumab New Zealand datasheet.
4. Patients who have been evaluated for tuberculosis risk factors/exposure for active/latent tuberculosis infection (per local requirements and according to the approved adalimumab New Zealand Datasheet).
5. Subject has voluntarily signed and dated an informed consent form, prior to any study-specific procedures.

### **9.2.2 Exclusion Criteria:**

1. Previous treatment with adalimumab
2. Previous treatment with any biologic
3. Severe infection including sepsis, active tuberculosis or opportunistic infection.
4. Moderate to severe heart failure (New York Heart Association Class II/III)
5. Concurrent administration with anakinra
6. Hypersensitivity to adalimumab or its excipients
7. Any condition that in the opinion of the investigator would compromise the subject's well-being or ability to perform the study requirements.

The duration of the study will be up to 6 months. Study visits are Screening/Baseline (Day 1) and 2 months, 4 months and 6 months.

There is a  $\pm$  seven (7) day window for all study visits. An effort will be made to bring subjects back to their original scheduled visit (calculated from Baseline) if they are out of the visit window for more than one visit.

For subjects who discontinue from the study prematurely a phone call will be made 30 days after the last dose of adalimumab is administered to obtain follow-up information on any ongoing or new adverse events.

### **9.2.3 Discontinuation of Individual Subjects:**

Each subject has the right to withdraw from the study at any time. In addition, the investigator may discontinue a subject from the study at any time if the investigator considers it necessary for any reason, including the occurrence of an adverse event. If the reason for treatment discontinuation is due to a serious adverse event, it should be reported to AbbVie within 24 hours of physician's awareness.

In the event that a subject withdraws or is discontinued from the study, the primary reason for discontinuation and any other reason(s) for the discontinuation from the study will be recorded. Following discontinuation of the study drug, the patient will be treated in accordance with the Investigator's best clinical judgment.

For subjects who discontinue from the study prematurely a phone call will be made 30 days after the last dose of adalimumab is administered to obtain follow-up information on any ongoing or new adverse events.

Subjects will be withdrawn from the study immediately if any of the following occur:

- The investigator believes it is in the best interest of the subject.
- The subject or subject's guardian requests withdrawal from the study.
- A selection criteria violation was noted after the subject started study drug.

### **9.3 Investigator Selection Criteria**

Selection of investigators will be made based on qualification by training and experience. Confirmation of adequate resources to properly conduct the trial according to the protocol will be obtained through site evaluation/selection visit prior to study initiation and a signed copy of the investigator agreement page of this protocol.

### **9.4 Variables**

The primary outcome variable is change in WHODAS 2.0 response score at 6 months compared to Baseline.

Secondary outcome variables include WHODAS 2.0 response score at 2 and 4 months compared to Baseline and other PRO scores of work activity and well-being at all study time points compared to Baseline.



Pre-specified safety variables include subject demographics (age, ethnicity, smoking status etc.) serious adverse events (SAEs), adverse events, adverse events leading to discontinuation, concomitant vital signs, and pregnancy outcomes.

## 9.5 Data Sources

Designated investigator staff will collect data required by the protocol on paper Case Report Forms (CRFs). Collection of data includes but not limited to subject demographics, adverse events, serious adverse events and concomitant medications. Designated investigator staff should not enter any data until they have completed appropriate training. The sites are requested to send a copy of the CRF (scanned copy is acceptable) through to the Data Manager to enter into the database within 10 working days. Where there are discrepancies with the data, data clarification forms should be raised for the designated investigator staff to clarify and return to the Sponsor.

### 9.5.1 Questionnaires:

Subject self-assessment questionnaires will be utilized in this study to determine patients' improvement over time. Patients will require Internet access as the questionnaires are administered electronically through an online portal. For patients unable to utilize the online questionnaires paper-and-pencil versions of questionnaires will be provided and can be self-administered in person in a quiet and private area of the clinic. In addition, for subjects completing paper and pencil versions, the questionnaires can be administered over the telephone if the questionnaire time-point does not coincide with a clinic visit. Data collected via paper and pencil versions of the questionnaires will be transcribed by site staff into the online portal on behalf of the patient. Data will be retrieved directly by the Data Manager for analysis. Based on a pilot evaluation of the study questionnaires in a small number of patients, they are expected to take approximately 10 minutes per visit, per subject, to administer. Patients should ensure that their subject number and the date the questionnaire was completed is entered onto the questionnaire.

Each patient will complete six (6) common questionnaires at Baseline, Month 2, Month 4 and Month 6:

- WHODAS 2.0
  - Covers six different domains: cognition, mobility, self-care, getting along, life activities and participation.
  - Does not have a set cut point to define disability
  - 12 items

- 
- WPAI:GH V2.0
    - This questionnaire looks at the effect of health problems on ability to work and perform regular activities.
    - Time missed from work, impairment of work
    - 6 items
  - K10
    - Intended to yield a global measure of distress based on questions about anxiety and depressive symptoms that a person has experienced in the most recent 4 week period.
    - Strong psychometric properties
    - 10 items
  - Flourishing Scale
    - Eight items describing important aspects of human functioning ranging from positive relationships, to feelings of competence, to having meaning and purpose in life.
  - Subject Vitality Scale
    - The state of feeling alive and alert - to having energy available to the self.
    - 7 items
  - A Disease-Specific patient reported outcome questionnaire:
    - HAQ-DI for patients with rheumatoid arthritis
      - Developed as a comprehensive measure of functional status in patients with a wide variety of rheumatic diseases
      - 15 items
    - SIBDQ for patients with Crohn's disease
      - The SIBDQ is a simple, validated, 10 item questionnaire, taken from the original 32 question IBDQ, that can be easily scored and interpreted by clinicians.
      - 10 items
    - DLQI for patients with psoriasis
      - Has been used in over 40 different skin conditions
      - Most frequently used instrument in studies of randomised controlled trials in dermatology.
      - 10 items

The WHODAS 2.0 will be used to assess the primary endpoint. The WHODAS 2.0 and all other questionnaires will be used to assess the secondary endpoints.

## **9.5.2 Physician completed assessments**

In accordance with the requirements for application for renewal of subsidy by Special Authority, a measure of disease activity will be administered within 3–6 months of initiation.

## **9.6 Study Size**

It is anticipated that the three groups will respond differently to adalimumab treatment over the study period and there is reason to believe that these groups will be different at baseline. Therefore, the sample size will be powered for rheumatoid arthritis and Crohn's disease. Approximately 80 subjects will be enrolled into each of these 2 parallel study groups allowing for detection of within participant effect sizes of approximately 0.40 as statistically significant (2-tailed  $\alpha=0.05$ ) with 90% power. A minimum of 30 subjects with psoriasis will also be enrolled. A minimum number of 190 patients will be enrolled into the study. The maximum number of rheumatoid arthritis and Crohn's disease patients will be N=100 in each arm, respectively.

Psoriasis patients make up a much smaller proportion of the population who currently receive adalimumab therapy in New Zealand. Therefore, a smaller number of patients (N=30) are sought to be enrolled in this study to ensure the trial population is representative of the general patient population. The maximum number of psoriasis patients will be N=50.

## **9.7 Data Management**

### **9.7.1 Data Collection**

The Investigator must maintain required records on all study subjects. Data for this study will be recorded in the subject's medical records, study-specific worksheets, CRFs and on electronic patient questionnaires provided by Sponsor. All data on the CRFs should be recorded with appropriate source documentation. Upon study completion or at any other time specified by the sponsor, a monitor will verify the source documentation records and review the data, under the responsibility and authority of the Investigator. The monitor will collect the appropriate CRF pages and a complete set of copies will remain at the investigational site with any related data clarification forms (DCF).

### **9.7.2 Data Correction**

Corrections of data entered on original source documents and CRFs must be made in the following manner:

- The incorrect entry must be crossed-out with a single line. The correct data should then be entered next to the entry crossed-out. Each correction, change or addition of new data must be initialed and dated by the individual making the correction / alteration.
- Completed source document/CRFs should be ready for review by the Sponsor monitor approximately within a week of each study visit for a given subject, unless the forms are incomplete because of laboratory data or adverse event follow-up that is not yet available.
- The Sponsor will review the source documents/CRFs, evaluate them for completeness and accuracy, and ensure all corrections are made to either the CRF or other designated clarification form.
- Any changes made to the CRF after collection by the Sponsor monitor will be discussed and approved by the Investigator (or designee) and corrected on a DCF.

### **9.7.3 Source Documentation**

Investigators must keep accurate separate records (other than the CRFs) of all subjects' visits, being sure to include all pertinent study related information. A statement should be made indicating that the subjects have been enrolled in Protocol and have provided written Informed Consent. Any and all side effects and adverse events must be thoroughly documented. Telephone conversations with the subjects concerning the study must also be recorded.

The Investigator is responsible for maintaining a Subject Identification Log, which will include all subjects who provided informed consent (i.e. to include randomized subjects and screening failures). This confidential subject identification code provides the link between named subject source records in the subject file and anonymous CRF and questionnaire data provided to the sponsor

The Investigator must retain all study related documentation until at least two years after at least two years have elapsed since the formal discontinuation of the clinical study. Study documents should not be destroyed without prior written agreement between the

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Investigator and the sponsor. The sponsor must be notified if the Investigator wishes to assign the study records to another party, or move them to another location.

## **9.8 Data Analysis**

### **9.8.1 Definitions**

#### **9.8.1.1 Participant Population**

All participants who are recruited into the study and start study medication will be used for analysis. A full analysis set will be used for the analysis of the efficacy outcomes with all available data used for the analyses of each outcome at the relevant time points. Efficacy measures are not assessed after a participant discontinues adalimumab. The exception to this will be the analysis of proportion of patients at 6 months who remain on adalimumab, having satisfied the requirements for application for renewal of subsidy by Special Authority. Any participants for whom this assessment is not available will be assumed to have not met these requirements. The primary population for the evaluation of study safety objectives will be the safety population, defined as all participants enrolled into the trial who started study medication. Safety outcomes will only be considered while the patient is on adalimumab. A standard consort diagram describing participant flow (including loss to follow-up and discontinuations for any reason) through the study will be generated.

#### **9.8.1.2 Observational Period**

The observational period will be from participant enrolment to 6 months or until any participant stops study medication or withdraws from the study.

### **9.8.2 Statistical Analyses**

The primary analysis of study efficacy measures will be performed using the full analysis set.

Tables showing standard descriptive statistics (including means, standard deviations, standard errors, medians, ranges and frequencies and percentages), graphs, and participant data listings will be used to summarize the baseline demographic and clinical characteristics, and the efficacy and safety data at relevant time-points. Tabular and graphical summaries will represent data separately for each indication group.

### **9.8.3 Demographic and Baseline Characteristics**

Participant demographic and baseline clinical characteristics will be summarized descriptively by indication group. No hypothesis testing will be performed for these summaries.

### **9.8.4 Primary Efficacy Analyses**

The primary efficacy outcome is the change in the total WHODAS 2.0 score at 6 months after the initiation of adalimumab, across all indication groups. This change will be summarised as the mean and 95% confidence interval and will be tested with a general linear model which includes participant, indication and baseline WHODAS 2.0 score as terms in the analysis.

### **9.8.5 Secondary Efficacy Analyses**

The following secondary endpoints will be analysed and summarised using general linear models and paired t-tests. The analyses summarising the changes across all indications will include participant, baseline levels and indication as terms in the analyses. Those analyses analysing changes within indications will use paired t-tests. Mean changes will be summarised with 95% confidence intervals derived from these analyses.

- Change in total WHODAS score 2 and 4 months after the initiation of adalimumab across all indications
- Change in total WHODAS score 6 months after the initiation of adalimumab in each indication
- Changes in WPAI:GI, K10, Flourishing Scale, and Subject Vitality Scale scores at 2, 4 and 6 months after the initiation of adalimumab, across all indications

- Change in disease-specific scores (HAQ-DI, SIBDQ, DLQI) at 2, 4 and 6 months after the initiation of adalimumab, in each indication

The proportion of patients at 6 months who remain on adalimumab, having satisfied the requirements for application for renewal of subsidy by special authority as defined below for each indication will be summarised for all indications combined and separately. These proportions will be summarised with exact 95% confidence intervals.

- **Rheumatoid arthritis:**  $\geq 50\%$  decrease in active joint count from baseline AND a clinically significant response to treatment in the opinion of the physician
- **Crohn's disease:** CDAI score reduction by 100 points or CDAI score  $\leq 150$
- **Psoriasis:** PASI score reduction of  $\geq 75\%$ ; or in the case of a patient had severe chronic plaque psoriasis of the face, or palm of a hand or sole of a foot at the start of treatment, the patient has a reduction in the PASI symptom subscores for all 3 of erythema, thickness and scaling, to slight or better, OR  $\geq 75\%$  reduction in affected skin area.

### 9.8.6 Safety Analyses

Adverse events occurring while participants are on adalimumab will be coded using CTCAE classification individually listed by indication groups. The incidences and percentages of individuals experiencing AEs and SAEs within each indication will be summarized by System Organ Class (SOC) with further summaries by severity and relatedness (causality) categories. Adverse events leading to discontinuation and concomitant medications will also be listed and summarised.

### 9.8.7 Additional Analyses

Additional analyses will explore the potential modifying effects of baseline measures on the changes in primary and secondary efficacy outcomes. These measures will include age, gender, baseline severity, and other diagnoses/co-morbidities. The analyses will specifically test for differential changes across the subgroups defined by the potential modifiers using general linear models. Further analyses will explore changes in the

subscales of some of the efficacy measures, for example the six major life domains of the total WHODAS score.

## **9.9 Missing Data**

Efficacy measures are not assessed after a participant discontinues adalimumab. The exception to this will be the analysis of proportion of patients at 6 months who remain on adalimumab, having satisfied the requirements for application for renewal of subsidy by special authority. Any participants for whom this assessment is not available will be assumed to have not met these requirements. There will be no other imputation for missing data.

## **9.10 Interim Analysis**

An interim analysis will be conducted at the time point indicated in the study milestones section (6.0) on data from all patients who have completed the study up to and including the 6 month time-point. This analysis will analyse and summarise the changes in the primary and secondary efficacy endpoints and the safety data. The results of this analysis will not influence the ongoing conduct of the study.

## **9.11 Quality Control**

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centres, review of protocol procedures with the investigator and associated personnel before the study and periodic monitoring visits by the sponsor. Written instructions will be provided for administration and collection of study questionnaires.

Guidelines for CRF completion will be provided and reviewed with study personnel before the start of the study. The sponsor will review CRFs and subject questionnaires for accuracy and completeness during on-site monitoring visits and after transmission to the sponsor; any discrepancies will be resolved with the investigator or designee, as appropriate. After upload of the data into the clinical study database they will be verified for accuracy and consistency with the data sources.



**9.12 Limitations of the Research Methods****9.13 Other Aspects****9.13.1 Note To File**

The Principal Investigator or designee will be responsible for documenting study relevant information and occurrences that affects the course of the study. The information and occurrences are not protocol deviations but will be documented in a note to file and will be communicated to the sponsor.

**9.13.2 Training Log**

All designated study personnel must be trained on the study protocol and procedures. Training and retraining are documented on the Training Log.

**9.13.3 Visitor Log**

All Sponsor or other related individuals who visit the study site must sign the Visitor Log.

**9.13.4 Responsibilities of the Principal Investigator**

The Principal Investigator is responsible for oversight of enrollment, the patient consent process, study related procedures, compliance with the protocol, all institutional, state and local guidelines.

It is the responsibility of the Principal Investigator to select, supervise, and delegate responsibility for study conduct to staff members. The Principal Investigator is responsible for determining the appropriate staff qualifications required for specific study-related tasks to be delegated. Study-related tasks delegated to staff members will be documented on the Site Signature and Delegation Log.

**9.13.5 End of Trial**

End of Trial is defined as last subject's last visit (LPLV).

## **10.0 Protection of Human Subjects**

This study must be conducted in compliance with the recommendations of the Declaration of Helsinki, 2008 (World Medical Association). In addition, this study will adhere to all general and local legal and regulatory requirements applicable to non-interventional studies.

Informed consent will be obtained from each subject before the subject can participate in the study. The contents and process of obtaining informed consent will be in accordance with all applicable regulatory requirements.

As required by applicable local regulations, the sponsor's Regulatory Affairs group will ensure all legal regulatory aspects are covered, and obtain approval of the appropriate regulatory bodies, prior to study initiation in regions where an approval is required.

This study is non-interventional and falls outside the scope of the EU Directive 2001/20/EC, the EU Directive 2005/28/EC and International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines.

This study complies with the EU Directive 95/46/EC of the European Parliament and of the Council of 24 October 1995 on the protection of individuals with regard to the processing of personal data and on the free movement of such data.

## **11.0 Management and Reporting of Adverse Events/Adverse Reactions**

### **11.1 Adverse Event Definition and Serious Adverse Event Categories**

An adverse event (AE) is defined as any untoward medical occurrence in a patient, which does not necessarily have a causal relationship with their treatment. An adverse event 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 adverse event.

An elective surgery/procedure scheduled to occur during the study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (*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.

If an adverse event meets any of the following criteria, it is considered a serious adverse event (SAE):

<b>Death of Patient:</b>	An event that results in the death of a patient.
<b>Life-Threatening:</b>	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.
<b>Hospitalization:</b>	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.
<b>Prolongation of Hospitalization:</b>	An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
<b>Congenital Anomaly:</b>	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
<b>Persistent or Significant Disability/Incapacity:</b>	An event that results in a condition that substantially interferes with the activities of daily living of a study patient. 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).
<b>Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:</b>	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 patient and may require medical or surgical intervention to prevent any of the outcomes listed above (i.e., death of patient, life threatening, hospitalization, prolongation of hospitalization, congenital anomaly, or persistent or significant disability/incapacity). Additionally, any elective or

spontaneous abortion or stillbirth is considered an important medical event. 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.

## 11.2 Severity

The following definitions will be used to rate the severity for any adverse event being collected as an endpoint/data point in the study and for all serious adverse events.

<b>Mild:</b>	The adverse event is transient and easily tolerated by the patient.
<b>Moderate:</b>	The adverse event causes the patient discomfort and interrupts the patient's usual activities.
<b>Severe:</b>	The adverse event causes considerable interference with the patient's usual activities and may be incapacitating or life threatening.

## 11.3 Relationship to Pharmaceutical Product

The following definitions will be used to assess the relationship of the adverse event to the use of product:

<b>Reasonable Possibility</b>	An adverse event where there is evidence to suggest a causal relationship between the product and the adverse event.
<b>No Reasonable Possibility</b>	An adverse event where there is no evidence to suggest a causal relationship between the product and the adverse event.

If no reasonable possibility of being related to product is given, an alternate etiology must be provided for the adverse event.

#### **11.4 Serious Adverse Event Collection Period**

Serious adverse events will be reported to AbbVie from the time the physician obtains the patient's authorization to use and disclose information (or the patient's informed consent) until 30 days or 5 half-lives following the intake of the last dose of physician-prescribed treatment.

#### **11.5 Serious Adverse Event Reporting**

In the event of a serious adverse event, and additionally, any non-serious event of malignancy in patients 30 years of age and younger, whether related to study drug or not, the Investigator will notify AbbVie Drug Safety [REDACTED]

[REDACTED] within 24 hours of the site being aware of the event.

#### **11.6 Pregnancy Reporting**

In the event of a pregnancy occurrence in the patient, the physician will notify AbbVie Drug Safety [REDACTED]

[REDACTED] identified within 24 hours of the physician becoming aware of the pregnancy.

#### **12.0 Plans for Disseminating and Communicating Study Results**

At the end of the study, a report will be written by AbbVie. This report will contain a description of the objectives of the study, the methodology and its results and conclusions. The completed Data Recording Forms, Questionnaires and the study report are the confidential property of AbbVie and may not be released to unauthorized people in any form (publications or presentations) without the express written approval from AbbVie. The results of this PMOS may be published by AbbVie Limited or by any one of the participating investigators after agreement with AbbVie Limited.

## 13.0 References

- (1) World Health Organisation. Disability Fact Sheet. Available at: <http://www.who.int/mediacentre/factsheets/fs352/en/#> Accessed 04-DEC-2014.
- (2) World Health Organisation 2011. World Report On Disability. Available at: <http://www.who.int>. Accessed 04-DEC-2014.
- (3) Scott DL, *et al.* *Lancet* 2010 Sep 25;376(9746):1094-108
- (4) Kalla R, *et al.* *BMJ* 2014 Nov 19;349:g6670. doi: 10.1136/bmj.g6670
- (5) Griffiths C, *et al.* *Lancet* 2007;370, Issue 9583, 21–27 July 2007:263-271
- (6) AbbVie Limited. Humira Data Sheet. 27 November 2014, Version 32. Available at [www.medsafe.govt.nz](http://www.medsafe.govt.nz) Accessed 04-DEC-2014
- (7) World Health Organisation. (2010). World Health Organization Disability Assessment Schedule 2.0. Retrieved from [http://www.who.int/classifications/icf/WHODAS2.0\\_12itemsINTERVIEW.pdf](http://www.who.int/classifications/icf/WHODAS2.0_12itemsINTERVIEW.pdf)
- (8) Reilly, M. C., *et al.* *Pharmacoeconomics*, 1993;4(5):353-365.
- (9) Kessler R.C., *et al.* *Archives General Psychiatry* 2003;60(2):184-189.
- (10) Diener E., Biswas-Diener R. (2009), Flourishing Scale. Retrieved from <http://internal.psychology.illinois.edu/~ediener/Documents/FS.pdf>
- (11) Ryan, R. M., & Frederick, C. M. *Journal of Personality* 1997;65:529-565.
- (12) Fries, J. F., *et al.* *Arthritis & Rheumatism* 1980;23(2):137-145.
- (13) Irvine, E.J., *et al.* *American Journal of Gastroenterology* 1996;91(8):1571.
- (14) Finlay, A.Y., Khan, G.K. *Clinical and Experimental Dermatology* 1994;19:210–216.

## Annex 1. Study Questionnaires

### A. WHODAS 2.0 questionnaire 12-item version, self-administered

The World Health Organization Disability Assessment Schedule (WHODAS 2.0) is a generic assessment instrument developed to provide a standardized method for measuring health and disability across cultures. It was developed from a comprehensive set of International Classification of Functioning, Disability and Health (ICF) items that are sufficiently reliable and sensitive to measure the difference made by a given intervention. This is achieved by assessing the same individual before and after the intervention.

WHODAS 2.0 has been found to be useful for assessing health and disability levels in the general population through surveys and for measuring the clinical effectiveness and productivity gains from interventions.

WHODAS 2.0 captures the level of functioning in six domains of life:

- Domain 1: Cognition – understanding and communicating
- Domain 2: Mobility – moving and getting around
- Domain 3: Self-care – attending to one’s hygiene, dressing, eating and staying alone
- Domain 4: Getting along – interacting with other people
- Domain 5: Life activities – domestic responsibilities, leisure, work and school
- Domain 6: Participation – joining in community activities, participating in society.

For all six domains, WHODAS 2.0 provides a profile and a summary measure of functioning and disability that is reliable and applicable across cultures, in all adult populations.

WHODAS 2.0 provides a common metric of the impact of any health condition in terms of functioning. Being a generic measure, the instrument does not target a specific disease – it can thus be used to compare disability due to different diseases. WHODAS 2.0 also makes it possible to design and monitor the impact of health and health-related interventions. The instrument has proven useful for assessing health and disability levels in the general population and in specific groups (e.g. people with a range of different mental and physical conditions).

Aspects that make WHODAS 2.0 particularly useful are its sound theoretical underpinnings, good psychometric properties, numerous applications in different groups and settings, and ease of use. WHODAS 2.0 can be self-administered in around 5 minutes,



and administered through an interview in 20 minutes. The instrument is easy to score and interpret (Ustun, Kostanjsek, Chatterji, & Rehm, 2010).



## WHODAS 2.0

WORLD HEALTH ORGANIZATION  
DISABILITY ASSESSMENT SCHEDULE 2.0

### 12-item version, self-administered

This questionnaire asks about difficulties due to health conditions. Health conditions include diseases or illnesses, other health problems that may be short or long lasting, injuries, mental or emotional problems, and problems with alcohol or drugs.

Think back over the past 30 days and answer these questions, thinking about how much difficulty you had doing the following activities. For each question, please circle only one response.

In the past 30 days, how much difficulty did you have in:						
S1	Standing for <u>long periods</u> such as <u>30 minutes</u> ?	None	Mild	Moderate	Severe	Extreme or cannot do
S2	Taking care of your <u>household responsibilities</u> ?	None	Mild	Moderate	Severe	Extreme or cannot do
S3	<u>Learning a new task</u> , for example, learning how to get to a new place?	None	Mild	Moderate	Severe	Extreme or cannot do
S4	How much of a problem did you have <u>joining in community activities</u> (for example, festivities, religious or other activities) in the same way as anyone else can?	None	Mild	Moderate	Severe	Extreme or cannot do
S5	How much have <u>you</u> been <u>emotionally affected</u> by your health problems?	None	Mild	Moderate	Severe	Extreme or cannot do



In the past 30 days, how much difficulty did you have in:						
S6	<u>Concentrating</u> on doing something for <u>ten minutes</u> ?	None	Mild	Moderate	Severe	Extreme or cannot do
S7	<u>Walking a long distance</u> such as a <u>kilometre</u> [or equivalent]?	None	Mild	Moderate	Severe	Extreme or cannot do
S8	<u>Washing your whole body</u> ?	None	Mild	Moderate	Severe	Extreme or cannot do
S9	Getting <u>dressed</u> ?	None	Mild	Moderate	Severe	Extreme or cannot do
S10	<u>Dealing</u> with people <u>you do not know</u> ?	None	Mild	Moderate	Severe	Extreme or cannot do
S11	<u>Maintaining a friendship</u> ?	None	Mild	Moderate	Severe	Extreme or cannot do
S12	Your day-to-day <u>work</u> ?	None	Mild	Moderate	Severe	Extreme or cannot do

H1	Overall, in the past 30 days, <u>how many days</u> were these difficulties present?	<b>Record number of days</b> ____
H2	In the past 30 days, for how many days were you <u>totally unable</u> to carry out your usual activities or work because of any health condition?	<b>Record number of days</b> ____
H3	In the past 30 days, not counting the days that you were totally unable, for how many days did you <u>cut back</u> or <u>reduce</u> your usual activities or work because of any health condition?	<b>Record number of days</b> ____

This completes the questionnaire. Thank you.

## B. Kessler Psychological Distress Scale (K10)

This is a 10-item questionnaire intended to yield a global measure of distress based on questions about anxiety and depressive symptoms that a person has experienced in the most recent 4 week period.

### K10 Test

These questions concern how you have been feeling over the past 30 days. Tick a box below each question that best represents how you have been .

<b>1. During the last 30 days, about how often did you feel tired out for no good reason?</b>				
1. None of the time	2. A little of the time	3. Some of the time	4. Most of the time	5. All of the time

<b>2. During the last 30 days, about how often did you feel nervous?</b>				
1. None of the time	2. A little of the time	3. Some of the time	4. Most of the time	5. All of the time

<b>3. During the last 30 days, about how often did you feel so nervous that nothing could calm you down?</b>				
1. None of the time	2. A little of the time	3. Some of the time	4. Most of the time	5. All of the time

<b>4. During the last 30 days, about how often did you feel hopeless?</b>				
1. None of the time	2. A little of the time	3. Some of the time	4. Most of the time	5. All of the time

<b>5. During the last 30 days, about how often did you feel restless or fidgety?</b>				
1. None of the time	2. A little of the time	3. Some of the time	4. Most of the time	5. All of the time

<b>6. During the last 30 days, about how often did you feel so restless you could not sit still?</b>				
1. None of the time	2. A little of the time	3. Some of the time	4. Most of the time	5. All of the time

<b>7. During the last 30 days, about how often did you feel depressed?</b>				
1. None of the time	2. A little of the time	3. Some of the time	4. Most of the time	5. All of the time

<b>8. During the last 30 days, about how often did you feel that everything was an effort?</b>				
1. None of the time	2. A little of the time	3. Some of the time	4. Most of the time	5. All of the time

<b>9. During the last 30 days, about how often did you feel so sad that nothing could cheer you up?</b>				
1. None of the time	2. A little of the time	3. Some of the time	4. Most of the time	5. All of the time

<b>10. During the last 30 days, about how often did you feel worthless?</b>				
1. None of the time	2. A little of the time	3. Some of the time	4. Most of the time	5. All of the time

## C. Health Assessment Questionnaire–Disability Index (HAQ-DI)

### HEALTH ASSESSMENT QUESTIONNAIRE (HAQ-DI)©

Name: \_\_\_\_\_ Date: \_\_\_\_\_

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
<b><u>DRESSING &amp; GROOMING</u></b>				
Are you able to:				
Dress yourself, including shoelaces and buttons?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Shampoo your hair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b><u>ARISING</u></b>				
Are you able to:				
Stand up from a straight chair?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Get in and out of bed?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b><u>EATING</u></b>				
Are you able to:				
Cut your own meat?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Lift a full cup or glass to your mouth?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Open a new milk carton?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b><u>WALKING</u></b>				
Are you able to:				
Walk outdoors on flat ground?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Climb up five steps?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

<input type="checkbox"/> Devices used for Dressing (button hook, zipper pull, etc.)	<input type="checkbox"/> Built up or special utensils	<input type="checkbox"/> Crutches
	<input type="checkbox"/> Cane	<input type="checkbox"/> Wheelchair
<input type="checkbox"/> Special or built up chair	<input type="checkbox"/> Walker	

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

<input type="checkbox"/> Dressing and grooming	<input type="checkbox"/> Arising	<input type="checkbox"/> Eating	<input type="checkbox"/> Walking
--	----------------------------------	---------------------------------	----------------------------------

Please place an "x" in the box which best describes your abilities OVER THE PAST WEEK:

	WITHOUT ANY DIFFICULTY	WITH SOME DIFFICULTY	WITH MUCH DIFFICULTY	UNABLE TO DO
<b><u>HYGIENE</u></b>				
Are you able to:				
Wash and dry your body?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Take a tub bath?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Get on and off the toilet?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b><u>REACH</u></b>				
Are you able to:				
Reach and get down a 5 pound object (such as a bag of sugar) from above your head?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Bend down to pick up clothing from the floor?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b><u>GRIP</u></b>				
Are you able to:				
Open car doors?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Open previously opened jars?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Turn faucets on and off?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<b><u>ACTIVITIES</u></b>				
Are you able to:				
Run errands and shop?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Get in and out of a car?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Do chores such as vacuuming or yard work?	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Please check any AIDS OR DEVICES that you usually use for any of the above activities:

<input type="checkbox"/> Raised toilet seat	<input type="checkbox"/> Bathtub bar	<input type="checkbox"/> Long-handled appliances for reach
<input type="checkbox"/> Bathtub seat	<input type="checkbox"/> Long-handled appliances in bathroom	<input type="checkbox"/> Jar opener (for jars previously opened)

Please check any categories for which you usually need HELP FROM ANOTHER PERSON:

<input type="checkbox"/> Hygiene	<input type="checkbox"/> Reach	<input type="checkbox"/> Gripping and opening things	<input type="checkbox"/> Errands and chores
----------------------------------	--------------------------------	--	---

**Your ACTIVITIES:** To what extent are you able to carry out your everyday physical activities such as walking, climbing stairs, carrying groceries, or moving a chair?

COMPLETELY	MOSTLY	MODERATELY	A LITTLE	NOT AT ALL
<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

**Your PAIN:** How much pain have you had IN THE PAST WEEK?

On a scale of 0 to 100 (where zero represents "no pain" and 100 represents "severe pain"), please record the number below.

--	--	--

**Your HEALTH:** Please rate how well you are doing on a scale of 0 to 100 (0 represents "very well" and 100 represents "very poor" health), please record the number below.

--	--	--

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### C. Short Quality of Life in Inflammatory Bowel Disease Questionnaire (IBDQ)

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

1. How often has the feeling of fatigue or being tired and worn out been a problem for you during the past 2 weeks?
  1. All of the time
  2. Most of the time
  3. A good bit of the time
  4. Some of the time
  5. A little of the time
  6. Hardly any of the time
  7. None of the time
2. How often during the last 2 weeks have you delayed or canceled a social engagement because of your bowel problem?
  1. All of the time
  2. Most of the time
  3. A good bit of the time
  4. Some of the time
  5. A little of the time
  6. Hardly any of the time
  7. None of the time
3. As a result of your bowel problems, how much difficulty did you experience doing leisure or sports activities you would have liked to have done during the past 2 weeks?
  1. A great deal of difficulty; activities made impossible
  2. A lot of difficulty
  3. A fair bit of difficulty
  4. Some difficulty
  5. A little difficulty
  6. Hardly any difficulty
  7. No difficulty; the bowel problem did not limit sports or leisure activities
4. How often during the past 2 weeks have you been troubled by pain in the abdomen?
  1. All of the time
  2. Most of the time
  3. A good bit of the time
  4. Some of the time
  5. A little of the time

- 
- 6. Hardly any of the time
  - 7. None of the time
  - 5. How often during the past 2 weeks have you felt depressed or discouraged?
    - 1. All of the time
    - 2. Most of the time
    - 3. A good bit of the time
    - 4. Some of the time
    - 5. A little of the time
    - 6. Hardly any of the time
    - 7. None of the time
  - 6. Overall, in the past 2 weeks, how much of a problem have you had with passing large amounts of gas?
    - 1. A major problem
    - 2. A big problem
    - 3. A significant problem
    - 4. Some problem
    - 5. A little trouble
    - 6. Hardly any trouble
    - 7. No trouble
  - 7. Overall, in the past 2 weeks, how much of a problem have you had maintaining or getting to the weight you would like to be?
    - 1. A major problem
    - 2. A big problem
    - 3. A significant problem
    - 4. Some problem
    - 5. A little trouble
    - 6. Hardly any trouble
    - 7. No trouble
  - 8. How often during the past 2 weeks have you felt relaxed and free of tension?
    - 1. All of the time
    - 2. Most of the time
    - 3. A good bit of the time
    - 4. Some of the time
    - 5. A little of the time
    - 6. Hardly any of the time
    - 7. None of the time
  - 9. How much of the time during the past 2 weeks have you been troubled by a feeling of having to go to the bathroom even though your bowels were empty?
    - 1. All of the time
    - 2. Most of the time
-

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

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

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

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## D. Dermatology Life Quality Index

**DERMATOLOGY LIFE QUALITY INDEX**

Hospital No:	Date:	Score:	<b>DLQI</b> <div style="border: 1px solid black; width: 40px; height: 20px; margin: 0 auto;"></div>
Name:	Diagnosis:		
Address:			

**The aim of this questionnaire is to measure how much your skin problem has affected your life OVER THE LAST WEEK. Please tick ☐ one box for each question.**

1. Over the last week, how itchy, sore, painful or stinging has your skin been?	Very much <input type="checkbox"/> A lot <input type="checkbox"/> A little <input type="checkbox"/> Not at all <input type="checkbox"/>	
2. Over the last week, how embarrassed or self conscious have you been because of your skin?	Very much <input type="checkbox"/> A lot <input type="checkbox"/> A little <input type="checkbox"/> Not at all <input type="checkbox"/>	
3. Over the last week, how much has your skin interfered with you going shopping or looking after your home or garden?	Very much <input type="checkbox"/> A lot <input type="checkbox"/> A little <input type="checkbox"/> Not at all <input type="checkbox"/>	Not relevant <input type="checkbox"/>
4. Over the last week, how much has your skin influenced the clothes you wear?	Very much <input type="checkbox"/> A lot <input type="checkbox"/> A little <input type="checkbox"/> Not at all <input type="checkbox"/>	Not relevant <input type="checkbox"/>
5. Over the last week, how much has your skin affected any social or leisure activities?	Very much <input type="checkbox"/> A lot <input type="checkbox"/> A little <input type="checkbox"/> Not at all <input type="checkbox"/>	Not relevant <input type="checkbox"/>
6. Over the last week, how much has your skin made it difficult for you to do any sport?	Very much <input type="checkbox"/> A lot <input type="checkbox"/> A little <input type="checkbox"/> Not at all <input type="checkbox"/>	Not relevant <input type="checkbox"/>
7. Over the last week, has your skin prevented you from working or studying?	Yes <input type="checkbox"/> No <input type="checkbox"/>	Not relevant <input type="checkbox"/>
If "No", over the last week how much has your skin been a problem at work or studying?	A lot <input type="checkbox"/> A little <input type="checkbox"/> Not at all <input type="checkbox"/>	
8. Over the last week, how much has your skin created problems with your partner or any of your close friends or relatives?	Very much <input type="checkbox"/> A lot <input type="checkbox"/> A little <input type="checkbox"/> Not at all <input type="checkbox"/>	Not relevant <input type="checkbox"/>
9. Over the last week, how much has your skin caused any sexual difficulties?	Very much <input type="checkbox"/> A lot <input type="checkbox"/> A little <input type="checkbox"/> Not at all <input type="checkbox"/>	Not relevant <input type="checkbox"/>
10. Over the last week, how much of a problem has the treatment for your skin been, for example by making your home messy, or by taking up time?	Very much <input type="checkbox"/> A lot <input type="checkbox"/> A little <input type="checkbox"/> Not at all <input type="checkbox"/>	Not relevant <input type="checkbox"/>

**Please check you have answered EVERY question. Thank you.**

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**E. Work Productivity and Activity Impairment Questionnaire: General Health  
V2.0 (WPAI:GH)**

The following questions ask about the effect of your health problems on your ability to work and perform regular activities. By health problems we mean any physical or emotional problem or symptom. *Please fill in the blanks or circle a number, as indicated.*

1. Are you currently employed (working for pay)? \_\_\_\_\_NO \_\_\_\_\_YES

*If NO, check "NO" and skip to question 6.*

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

2. During the past seven days, how many hours did you miss from work because of your health problems? *Include hours you missed on sick days, times you went in late, left early, etc., because of your health problems. Do not include time you missed to participate in this study.*  
\_\_\_\_\_HOURS
3. During the past seven days, how many hours did you miss from work because of any other reason, such as vacation, holidays, time off to participate in this study?  
\_\_\_\_\_HOURS
4. During the past seven days, how many hours did you actually work?  
\_\_\_\_\_HOURS (If "0," skip to question 6.)
5. During the past seven days, how much did your health problems 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 health problems affected your work only a little, choose a low number. Choose a high number if health problems affected your work a great deal.*

Consider only how much health problems affected  
productivity while you were working.

Health problems had  
no effect on my  
work

0 1 2 3 4 5 6 7 8 9 10

Health problems  
completely prevented  
me from working

CIRCLE A NUMBER

6. During the past seven days, how much did your health problems 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 health problems affected your activities only a little, choose a low number. Choose a high number if health problems affected your activities a great deal.*

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

Health problems had  
no effect on my daily  
activities

0 1 2 3 4 5 6 7 8 9 10

Health problems  
completely prevented  
me from doing my  
daily activities

CIRCLE A NUMBER

## F. Flourishing Scale

The Flourishing Scale consists of eight items describing important aspects of human functioning ranging from positive relationships, to feelings of competence, to having meaning and purpose in life. The scale was called Psychological Well-being in an earlier publication, but the name was changed to more accurately reflect the content because the scale includes content that goes beyond psychological well-being narrowly defined.

### Flourishing Scale

Below are eight statements with which you may agree or disagree. Using the scale provided, indicate your agreement with each statement by choosing the appropriate score.

- 7 = Strongly agree
- 6 = Agree
- 5 = Slightly agree
- 4 = Neither agree nor disagree
- 3 = Slightly disagree
- 2 = Disagree
- 1 = Strongly disagree

1. I lead a purposeful and meaningful life \_\_\_\_\_
2. My social relationships are supportive and rewarding \_\_\_\_\_
3. I am engaged and interested in my daily activities \_\_\_\_\_
4. I actively contribute to the happiness and well-being of others \_\_\_\_\_
5. I am competent and capable in the activities that are important to me \_\_\_\_\_
6. I am a good person and live a good life \_\_\_\_\_
7. I am optimistic about my future \_\_\_\_\_
8. People respect me \_\_\_\_\_

**Total** \_\_\_\_\_

## G. Subjective Vitality Scale

The concept of subjective vitality refers to the state of feeling alive and alert - to having energy available to the self.

### Subjective Vitality Scale

Please rate the follow items in regard to how they "apply to you and your life at the present time."

not at all true				somewhat true			very true
1	2	3	4	5	6	7	

- |   |       |
|---|-------|
| 1. I feel alive and vital                         | _____ |
| 2. I don't feel very energetic                    | _____ |
| 3. Sometimes I feel so alive I just want to burst | _____ |
| 4. I have energy and spirit                       | _____ |
| 5. I look forward to each new day                 | _____ |
| 6. I nearly always feel alert and awake           | _____ |
| 7. I feel energized                               | _____ |

<b>Total</b>	_____
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## Annex 2. Protocol Amendment: List of Changes

The summary of changes is listed in Section 1.1.

### **Specific Protocol Changes:**

#### **Title Page**

##### **Protocol title previously read:**

An Observational Study of the Effectiveness of Adalimumab on Health and Disability Outcomes in New Zealand Patients with Immune-Mediated Inflammatory Diseases

##### **Has been changed to read:**

An Observational Study of the Effectiveness of **Adalimumab** on Health and Disability Outcomes in New Zealand Patients with **Immune-Mediated Inflammatory Diseases (VITALITY)**

#### **Section 3.0 Responsible Parties**

##### **Study-Designated Physician**

Landline phone number has been deleted as it no longer exists.  
Email address specified.

#### **Section 4.0 Abstract**

##### **Subsection: Title**

##### **Previously read:**

An Observational Study of the Effectiveness of Adalimumab on Health and Disability Outcomes in New Zealand Patients with Immune-Mediated Inflammatory Diseases

##### **Has been changed to read:**

An Observational Study of the Effectiveness of **Adalimumab** on Health and Disability Outcomes in New Zealand Patients with **Immune-Mediated Inflammatory Diseases (VITALITY)**

#### **Section 4.0 Abstract**

##### **Subsection: Inclusion Criteria**

##### **Addition of text:**

---

Patients have been evaluated for tuberculosis risk factors/exposure for active/latent tuberculosis infection (per local requirements and according to the approved adalimumab New Zealand Datasheet).

## **Section 6.0 Milestones**

### **Previously read:**

Major study milestones and their planned dates are as follows:

Start of Data Collection (FPFV):	13 April 2015
End of Data Collection:	12 April 2016
Database Lock:	26 April 2016
Interim Database Lock:	01 December 2015
Interim Report:	01 February 2016
Final Report of Study Results:	07 June 2016

### **Has been changed to read:**

Major study milestones and their planned dates are as follows:

Start of Data Collection (FPFV):	06 July 2015
End of Data Collection:	06 September 2016
Database Lock:	20 September 2016
Interim Database Lock:	01 March 2016
Interim Report:	31 March 2016
Final Report of Study Results:	11 November 2016

## **Section 9.0 Research Methods**

### **Subsection 9.1 Study Design, Paragraph 3**

#### **Addition of text:**

AbbVie is not supplying adalimumab; adalimumab is to be used according to the approved adalimumab New Zealand Datasheet and is to be prescribed by the physician under usual and customary practice of physician prescription.

## **Section 9.0 Research Methods**

### **Subsection 9.1 Study Design, Paragraph 8**

**Previously read:**

No restriction on current standard of care is imposed. The use of any concomitant medication and any and all adverse events will be captured and recorded in the CRF.

**Has been changed to read:**

No restriction on current standard of care is imposed. Physicians should treat their patients as they would in their routine clinical practice. Prior medical history, the use of any concomitant medication and any and all adverse events will be captured and recorded in the CRF.

**Section 9.0 Research Methods**

**Subsection 9.1 Study Design, Following Paragraph 9**

**Addition of text:**

Prior to collecting any study related information, written informed consent must be obtained.

Each subject has the right to withdraw from the study at any time. In addition, the investigator may discontinue a subject from the study at any time if the investigator considers it necessary for any reason, including the occurrence of an adverse event or noncompliance with the protocol.

In the event that a subject withdraws or is discontinued from the study, the primary reason for discontinuation and any other reason(s) for the discontinuation from the study will be recorded. If the reason for treatment discontinuation is due to a serious adverse event, it should be reported to AbbVie within 24 hours of physician's awareness.

Subjects will be withdrawn from the study immediately if any of the following occur:

- The investigator believes it is in the best interest of the subject.
- The subject or subject's guardian requests withdrawal from the study.
- A selection criteria violation was noted after the subject started adalimumab.

The study procedures to be conducted (if part of routine clinical practice) are outlined in the schematic presented in Table 1

**Section 9.0 Research Methods**

**Subsection 9.1.1 Schedule of Events**



**Addition:** Row titled “Demographics” to table.

**Addition:** Footnote for “Demographics”:

† Once the physician has determined that the patient is eligible for inclusion, and the patient has agreed to be included in the observational study, the patient's demographic data (including year of birth, gender, ethnicity) will be recorded on the CRFs at the Baseline visit

**Addition:** Footnote for “Medical History”:

\*The physician will determine the patient's current health status and obtain a complete medical history including history of tobacco, date of diagnosis, disease activity, concomitant medications and TB exposure/risk factors at the Baseline visit.

**TB events previously read:**

Have record of a Purified Protein Derivative (PPD) test or Quantiferon Gold Test and a Chest X-Ray<sup>b</sup>

**Has been changed to read:**

TB History assessment

**Addition:** Footnote for “TB History assessment”:

An assessment of TB exposure/risk factors for active and latent TB (per local requirements and according to the approved adalimumab NZ Datasheet) must have been completed prior to the first dose of adalimumab with documented history of results

**Addition:** Footnote for “CRP”:

CRP will only be collected if procedure is performed as part of the usual standard of care

## Section 9.0 Research Methods

### **Addition of Subsection 9.1.3 Physician’s assessment of disease activity: Active joint count, or CDAI, or PASI**

An assessment of disease activity by the Physician will be recorded at the Baseline Visit and within 3–6 months of initiation, as per standard of care.

### **Addition of Subsection 9.1.3 PRO Questionnaires**

Patients will complete the following questionnaires at the visits identified on the Study Activities Table (Table 1).

- WHODAS 2.0
- WPAI:GH V2.0
- K10

- 
- Flourishing Scale
  - Subject Vitality Scale
  - A Disease-Specific patient reported outcome questionnaire:
    - o HAQ-DI for patients with rheumatoid arthritis
    - o SIBDQ for patients with Crohn's disease
    - o DLQI for patients with psoriasis

At the Baseline visit, the questionnaires must be completed before the first dose of adalimumab.

#### **Addition of Subsection 9.1.4 Adalimumab dosing**

The participating Physician will provide the patient with a prescription for adalimumab, along with instructions for appropriate use. The date of first dose of adalimumab will be recorded in the CRF and should closely align with the Baseline visit, but not before completion of the PRO questionnaires.

#### **Addition of Subsection 9.1.5 Product Supply**

Adalimumab will be obtained as commercially available medication. AbbVie will not provide the medication for this study.

### **Section 9.2 Setting**

#### **Paragraph 5**

#### **Addition of text:**

AbbVie is not supplying adalimumab; adalimumab is to be used according to the approved adalimumab New Zealand Datasheet and is to be prescribed by the physician under usual and customary practice of physician prescription.

### **Section 9.2 Setting**

#### **Subsection 9.2.1 Inclusion Criteria:**

#### **Addition of text:**

---

Patients who have been evaluated for tuberculosis risk factors/exposure for active/latent tuberculosis infection (per local requirements and according to the approved adalimumab New Zealand Datasheet).

### **Addition of Subsection 9.2.3 Discontinuation of Individual Subjects:**

Each subject has the right to withdraw from the study at any time. In addition, the investigator may discontinue a subject from the study at any time if the investigator considers it necessary for any reason, including the occurrence of an adverse event. If the reason for treatment discontinuation is due to a serious adverse event, it should be reported to AbbVie within 24 hours of physician's awareness.

In the event that a subject withdraws or is discontinued from the study, the primary reason for discontinuation and any other reason(s) for the discontinuation from the study will be recorded. Following discontinuation of the study drug, the patient will be treated in accordance with the Investigator's best clinical judgment.

For subjects who discontinue from the study prematurely a phone call will be made 30 days after the last dose of adalimumab is administered to obtain follow-up information on any ongoing or new adverse events.

Subjects will be withdrawn from the study immediately if any of the following occur:

- The investigator believes it is in the best interest of the subject.
- The subject or subject's guardian requests withdrawal from the study.
- A selection criteria violation was noted after the subject started study drug.

## **Section 9.5 Data Sources**

### **Previously read:**

Designated investigator staff will collect data required by the protocol on paper Case Report Forms (CRFs). Collection of data includes but not limited to subject demographics, adverse events, serious adverse events and concomitant medications. Designated investigator staff should not enter any data until they have completed appropriate training. These paper CRFs will be photocopied by the Sponsor or Sponsor Representative (CRA) and brought back for the Data Manager to enter into the database.

---

Where there are discrepancies with the data, data clarification forms should be raised for the designated investigator staff to clarify and return to the Sponsor

**Has been changed to read:**

Designated investigator staff will collect data required by the protocol on paper Case Report Forms (CRFs). Collection of data includes but not limited to subject demographics, adverse events, serious adverse events and concomitant medications. Designated investigator staff should not enter any data until they have completed appropriate training. The sites are requested to send a copy of the CRF (scanned copy is acceptable) through to the Data Manager to enter into the database within 10 working days. Where there are discrepancies with the data, data clarification forms should be raised for the designated investigator staff to clarify and return to the Sponsor.

**Section 9.5.1 Questionnaires**

**Paragraph 1**

**Previously read:**

Subject self-assessment questionnaires will be utilized in this study to determine patients' improvement over time. Patients will require Internet access as the questionnaires are administered electronically through an online portal. For patients unable to utilize the online questionnaires paper-and-pencil versions of questionnaires will be provided and can be self-administered in person in a quiet and private area of the clinic. In addition, for subjects completing paper and pencil versions, the questionnaires can be administered over the telephone if the questionnaire time-point does not coincide with a clinic visit. Data collected via paper and pencil versions of the questionnaires will be transcribed by site staff into the online portal on behalf of the patient. Data will be retrieved directly by the Data Manager for analysis. Based on a pilot evaluation of the study questionnaires in a small number of patients, they are expected to take approximately 10 minutes per visit, per subject, to administer.

**Has been changed to read:**

Subject self-assessment questionnaires will be utilized in this study to determine patients' improvement over time. Patients will require Internet access as the questionnaires are administered electronically through an online portal. For patients unable to utilize the online questionnaires paper-and-pencil versions of questionnaires will be provided and can be self-administered in person in a quiet and private area of the clinic. In addition, for subjects completing paper and pencil versions, the questionnaires can be administered over the telephone if the questionnaire time-point does not coincide with a clinic visit. Data collected via paper and pencil versions of the questionnaires will be transcribed by site staff into the online portal on behalf of the patient. Data will be retrieved directly by

the Data Manager for analysis. Based on a pilot evaluation of the study questionnaires in a small number of patients, they are expected to take approximately 10 minutes per visit, per subject, to administer. Patients should ensure that their subject number and the date the questionnaire was completed is entered onto the questionnaire.

## **Section 11.0 Management and Reporting of Adverse Events/Adverse Reactions**

### **Subsection 11.1 Adverse Event Definition and Serious Adverse Event Categories**

#### **Insertion of new paragraph directly following Paragraph 1:**

An elective surgery/procedure scheduled to occur during the study will not be considered an adverse event if the surgery/procedure is being performed for a pre-existing condition and the surgery/procedure has been pre-planned prior to study entry. However, if the pre-existing condition deteriorates unexpectedly during the study (*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 11.0 Management and Reporting of Adverse Events/Adverse Reactions**

### **Subsection 11.5 Serious Adverse Event Reporting**

#### **Previously read:**

In the event of a serious adverse event, the physician will:

- For events from patients using and AbbVie product - notify the AbbVie Emergency contact person identified below within 24 hours of the physician becoming aware of the event.

#### **Has been changed to read:**

In the event of a serious adverse event, and additionally, any non-serious event of malignancy in patients 30 years of age and younger, whether related to study drug or not, the Investigator will notify AbbVie Drug Safety (email [drugsafetyanz@abbvie.com](mailto:drugsafetyanz@abbvie.com) (preferred), fax: +61 2 6100 9780, or Ph: +61 2 9035 8640) within 24 hours of the site being aware of the event.

## **Section 11.0 Management and Reporting of Adverse Events/Adverse Reactions**

### **Subsection 11.6 Pregnancy reporting**

#### **Previously read:**

In the event of a pregnancy occurrence in the patient, the physician will notify AbbVie Emergency contact person identified within 24 hours of the physician becoming aware of the pregnancy.

**Has been changed to read:**

In the event of a pregnancy occurrence in the patient, the physician will notify AbbVie Drug Safety [REDACTED] identified within 24 hours of the physician becoming aware of the pregnancy.

**AbbVie Inc. (AbbVie)**  
**Post Marketing Observational Study**  
**Protocol P15-345**

**An Observational Study of the Effectiveness of Adalimumab on  
Health and Disability Outcomes in New Zealand Patients with  
Immune-Mediated Inflammatory Diseases**

Approved by:



23-OCT-2015

Date

22 OCT 2015

Date

03 NOV 2015

Date

abbvie

Adalimumab  
P15-345  
Protocol Amendment 1



Date

27 Oct 2015.

Date

28 OCT 2015

Date