Title Page

Title	Real-World Outcome of Adalimumab on Rheumatoid Arthritis Patients in China
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Procedure Number	Not applicable (Non-PASS PMOS)
Marketing Authorization Holder(s)	AbbVie Pharmaceutical Trading (Shanghai) Co. Ltd 17F, Chong Hing Finance Center 288 West Nanjing Road, Shanghai 200003
Joint PASS	Not applicable (Non-PASS PMOS)
Research Question and Objectives	The overall strategic objective of this non-interventional, observational study is to assess the effect of Adalimumab on health-related quality of life and work productivity in patients with Rheumatoid Arthritis (RA) in China.
Country(ies) of Study	China
Author	[redacted]

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 Authorization Holder(s)

Marketing Authorization Holder(s)	AbbVie Pharmaceutical Trading (Shanghai) Co. Ltd 17F, Chong Hing Finance Center 288 West Nanjing Road, Shanghai 200003
MAH Contact Person	Not applicable (Non-PASS PMOS)

1.0 Table of Contents

2.0 Abbreviations

ACR	**American College of Rheumatology**
AE	**Adverse Events**
ANOVA	**Analysis of Variance**
CRF	**Case Report Form**
CRP	**C-Reactive Protein**
CTCAE	**Common Terminology Criteria for Adverse Events**
DAS28	**Disease Activity Score in 28 Joints**
EQ-5D-3L	**EuroQol 5 dimension, 3 level quality of life questionnaire**
ESR	**Erythrocyte Sedimentation Rate**
EULAR	**The European League Against Rheumatism**
GP	**General Practitioner**
HAQ DI	**Health Assessment Questionnaire Disability Index**
HCRU	**Healthcare Resource Utilization**
ICF	**Informed Consent Form**
ICH-GCP	**International Conference on Harmonization of Good Clinical Practice**
NRS	**Numeric Rating Scale**
PGIC	**Patient Global Impression of Change**
PHI	**Protected Health Information**
PRO	**Patient-Reported Outcome**
QC	**Quality Check**
QoL	**Quality of Life**
RA	**Rheumatoid Arthritis**
SAP	**Statistical Analysis Plan**
SF-36	**Short Form 36-Item Health Survey**
SOC	**System Organ Class**
SOP	**Standard Operating Procedure**
TNF	**Tumor Necrosis Factor**
VAS	**Visual Analogue Scale**
WPAI	**Work Productivity and Activity Impairment**

3.0 Responsible Parties

Study-Designated Physician/ Sponsor:	[redacted]	
Affiliate Medical Director:		
Statistics:		
Principal Investigator:		
Sponsor:	**AbbVie Pharmaceutical Trading (Shanghai) Co. Ltd**	17F, Chong Hing Finance Center 288 West Nanjing Road, Shanghai 200003
Clinical Project Manager:	[redacted]	
Product complaint		
Emergency Contacts-Safety Review Team		

PROTOCOL SIGNATURES

Investigator Signature:

I have read and agree to the Protocol Number P15-776, "Real-World Outcome of Adalimumab on Rheumatoid Arthritis Patients in China". 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: Real-World Outcome of Adalimumab on Rheumatoid Arthritis Patients in China

Rationale and Background: Given the requirement to keep a balance between effectiveness and cost containment to ensure that the available health resources are used in a cost-effective manner, there is an increasing demand for real-world evidence (RWE) from policy makers, regulators, providers and payers in the region to optimize spending and patient outcomes.

So far, there are no data available regarding adalimumab's impact on patients' quality of life (QoL) and healthcare resource utilization (HCRU) in a realistic study design, which provides greater generalization in China.

The goal of this study is to determine the QoL, HCRU and costs of the patients care in subjects with RA who are treated with adalimumab in China.

Results from study on the effect of adalimumab on Work Productivity and Activity Impairment (WPAI) scores and other Patient-Reported Outcomes (PROs) will be of interest to a variety of stakeholders in the healthcare system including patients, healthcare practitioners and payers in China.

Research Question and Objectives: The objective of this non-interventional, observational study is to assess the effect of adalimumab on health-related QoL and work productivity in patients with Rheumatoid Arthritis (RA) in China. Specifically, to achieve the above objective the following concrete steps will be taken:

1. Recruit investigators who are willing and able to recruit and follow new adalimumab users for 6 months follow-up
2. Collect the patients' clinical profile, patient-reported QoL, functioning, work productivity, treatment satisfaction and HCRU of RA patients at adalimumab initiation
3. Follow the patients initiating adalimumab for 24 weeks and identify the changes in clinical, economic, and PROs associated with adalimumab

Study Design: The study is designed as a prospective, observational study to assess the effect of adalimumab on health-related QoL and work productivity in patients with RA in China.

RA patients, for whom adalimumab treatment has already been decided as per local label, will be recruited from within the clinical settings of each rheumatologist participating in the study. Approximately 52 patients diagnosed with RA that meet the inclusion and exclusion criteria will be enrolled at approximately 16 sites.

The Health Assessment Questionnaire Disability Index (HAQ DI) data will be collected at baseline, Week 12 and Week 24 after treatment initiation with adalimumab, as per standard daily clinical practice. In addition, when available, other PROs of work activity and well-being, including the WPAI, EuroQol 5 dimension (EQ-5D), and Short Form 36-Item Health Survey (SF-36), will also be collected.

In addition, when available, the health care resource utilization will be collected. This includes surgical procedures, hospitalizations, bed days in hospital, physician consultations etc. Costs will be assigned based on the health care resource utilization using standardized costs for China.

Note: This study is non-interventional and the subjects/investigators will follow the current clinical practice in each site and also the routine clinical follow up as determine by the treating physician.

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. Approximately 52 patients diagnosed with RA will be recruited.

Main Inclusion Criteria:
Patients meeting all of the following inclusion criteria at baseline will be included:

1. Subject has a diagnosis of RA as defined by the 1987 revised American College of Rheumatology (ACR) classification criteria and/or the ACR/the European League against Rheumatism (EULAR) 2010 classification criteria (any duration since diagnosis).
2. Male or female subjects ≥18 years of age who is in compliance with eligibility for adalimumab based on the local label.
3. Patients with moderate to severe RA defined as Disease Activity Score in 28 Joints (DAS28) (ESR) or DAS28 (CRP) >3.2
4. Biologically treatment naïve and initiated adalimumab at baseline visit, as per standard daily clinical practice.
5. Availability of clinical data of the previous 12 weeks prior to baseline
6. Ability to self-complete patient questionnaires
7. Patients have signed the authorization (or informed consent where applicable) to disclose and use personal health information after been prescribed with adalimumab.

Main Exclusion Criteria:

Patients meeting any of the following exclusion criteria at baseline will be excluded:

1. Patients who are pregnant or breast feeding at enrolment or wish to become pregnant in the next 24 weeks.
2. Participation in any RA-related clinical trial at the time of enrolment, at baseline or at any point during the past 24 weeks prior to baseline
3. Patients, who in the clinician's view, may not be able to accurately report their QoL or prior resource utilization
4. Patients, who in the clinician's view, may not be able to adhere to adalimumab therapy over 24 weeks.

Variables:

Primary Variable

- Change in HAQ DI score at week 24 from the baseline

Secondary Variable

- Change in HAQ DI score at week 12 from the baseline
- Change in other PROs (SF-36 domain scales, EQ-5D Index, Work Productivity and Activity Impairment Questionnaire [WPAI]) from baseline to weeks 12 and 24
- Number and percent of patients achieving a clinically meaningful improvement on the HAQ DI, from baseline to weeks 12 and 24

Additional Secondary Variable

- Change in HAQ DI score from baseline to week 24
- Changes in the disease severity and PROs from baseline to week 24
- Healthcare Resource Utilization (HCRU) at baseline, weeks 12 and 24

Exploratory Variable

- Change in patient satisfaction questions from baseline to weeks 12 and 24
- Patient's impression of change at weeks 12 and 24 from baseline

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

- EQ-5D
- SF-36
- HAQ DI
- WPAI
- HCRU
- Patient Global Impression of Change (PGIC)
- Patient Treatment Satisfaction Questions

Study Size: Approximately 52 patients diagnosed with RA that meet the inclusion and exclusion criteria will be enrolled at approximately 16 sites. The planned sample size provides 80% power for detecting a statistically significant improvement in HAQ-DI (Δ HAQ-DI < 0) assuming a mean ΔHAQ-DI of -0.21 and a standard deviation of 0.5

(reference 11), at two-sided significance level of 0.05 and accounting for a 10% dropout rate. The sample size also provides 99% power for detecting a statistically significant clinically meaningful improvement in HAQ-DI (ΔHAQ-DI < -0.22) assuming a mean ΔHAQ-DI of -0.5 and a standard deviation of 0.7, at two-sided significance level of 0.05 and accounting for a 10% dropout rate.

Data Analysis:
All the following analysis will be based on the data as observed.

Primary Endpoint Analysis
Change in HAQ DI score at week 24 after the initiation of adalimumab, in those patients continuing on adalimumab. This change will be summarized as the mean and 95% confidence interval and will be tested with a paired t-test.

Secondary Endpoint Analysis

- Change in HAQ DI score at week 12 after the initiation of adalimumab, in those patients continuing on adalimumab. This change will be summarized as the mean and 95% confidence interval and will be tested with a paired t-test.
- Change in other PROs (SF-36 domain scales, EQ-5D Index, WPAI total lost productivity) at weeks 12 and 24 after the initiation of adalimumab, in those patients continuing on adalimumab. These changes will be summarized as the means and 95% confidence intervals and will be tested with paired t-tests.
- Number and percent of patients achieving a clinically meaningful improvement on the HAQ DI, as defined by a -0.22 point improvement or greater, at weeks 12 and 24 after the initiation of adalimumab, in those patients continuing on adalimumab.

Additional Secondary Endpoint Analysis

- Change in HAQ DI score at week 24 after the initiation of adalimumab, in those patients continuing on adalimumab, compared with those patients not continuing on adalimumab. The mean changes in these two groups will be compared using an independent t-test.
- HCRU will be described using number and percentage within each category (number of consultations, number of procedures received, number of surgeries, number of hospitalizations and length of stay, number of concomitant medications)
- Associations between disease severity and PROs
- Associations between change in disease severity and change in PROs

Exploratory Endpoint Analysis

- Change in patient satisfaction questions at weeks 12 and 24 after the initiation of adalimumab, in those patients continuing on adalimumab. These changes will be summarized as number and percentage of each response and compared with Kruskal–Wallis test. Satisfaction will also be dichotomized and analyzed over time with Cochrane-Armitage test for trends.
- Patient's impression of change at weeks 12 and 24 after the initiation of adalimumab, in those patients continuing on adalimumab (as observed population). These changes will be summarized as number and percentage of each response and compared with Kruskal–Wallis test.

5.0 Amendments and Updates

Number	Date	Section of Study Protocol	Amendment or Update	Reason
P15-776	05/06/2015	n/a	Initial Protocol	n/a
P15-776	20/08/2015	Management and Reporting of Adverse Events/Adverse Reactions	Pediatric & Malignancy	As per the Protocol Guidance
P15-776	01/09/2015			Change from area study to affiliate study
P15-776	01/10/2015			Revise based on GMA-RC's comments
P15-776	02/23/2016			Revise based on new standard language, legal and investigators' comments
P15-776	08/07/2017	3.0 Responsible parties	Staff revised	Revised based on changes
P15-776	08/07/2017	6.0 Milestones	Timeline change	Revise based on enrollment progress
P15-776	08/07/2017	9.1 Study design	Sample size from 200 to 52	Revise based on enrollment progress
P15-776	08/07/2017	9.2 Setting	Sample size from 200 to 52	Revise based on enrollment progress
P15-776	08/07/2017	9.5 Study Size	Sample size reduced from 200 to 52 with power reduced to 80%; dropout rate reduced to 10%; remove WPAI as key factor for	Revise based on enrollment progress

			sample size	
P15-776	08/07/2017	9.2.3~12.7	Remove "IMS" or change "IMS" to "AbbVie" at appropriate places.	AbbVie is in charge of study operation.
P15-776	08/07/2017	12.5 Risks	Combine 12.5 and 12.6 and add subject insurance language.	Affiliate provides product liability insurance for PMOS.
P15-776	08/07/2017	Annexure	Remove all annexures and CRF.	Annexures not applicable for China. CRF is in a separate document.

6.0 Milestones

Major study milestones and their planned dates are as follows:

Start of Data Collection (FPFV):	15 April 2016
End of Data Collection:	30 June 2018
Study Progress Report:	Not Applicable
Registration in the EU PAS register:	Not Applicable
Final Report of Study Results:	31 December 2018

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.

For public health purposes disability is becoming increasingly important as an outcome measure. Despite this, no data, within our knowledge, on the effectiveness of adalimumab on health-related QoL and work productivity in patients with Rheumatoid Arthritis (RA) in China.

Results from study of effect of adalimumab on Work Productivity and Activity Impairment (WPAI) scores and other Patient-Reported Outcomes (PROs) 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 China.

The Chinese government has for some time been deeply concerned with an impending productivity fall associated with ageing and chronic illnesses, including musculoskeletal disorders. These concerns have a large impact on their health financing and structuring policies. Having the economic and health outcomes "real world evidence" (RWE) for the use of Humira in moderate RA patients will be helpful to fill in data gaps which will be valuable for Chinese Health Authorities.

In China, Humira is not listed on either provincial reimbursed drug list (PRDL) or national provincial reimbursed drug list (NRDL), which means that patients have to pay for the use of Humira. However, on August 30th, 2012, National Development and Reform Commission (NDRC), Ministry of Health (MOH) and other four ministries and commissions of China issued "Guidance about implementation of urban and rural residents' critical illness insurance (CDI) system". The CDI system aims to expand the coverage of the country's health care insurance system to include the treatment of critical illness, aiming to relieve urban and rural families of the heavy burden of catastrophic medical spending. By the end of August 2013, 94 regions across 23 provinces had piloted the critical illness cover system and seven provinces had fully implemented the system, benefiting 210 million people.

On Jan 2015, Humira was listed on the CDI in Qingdao. Patients with RA who are covered by CDI are reimbursed for 70 percent of the total costs. And on Oct 2015, Humira is also listed on the CDI in Shenzhen. Given CDI is new systems in China, the officials of CDI cities encourage company to collect the RWE associated with the use of Humira to further demonstrate the value of Humira to Chinese patients, especially in their local regions. The result will assist decision makers to evaluate the CDI from a broader perspective and to determine the value of continuing the program. In addition, generating RWE related the use of Humira in patients with RA will be extremely valuable for application of Humira on the CDI list in other provinces in China.

The objective of this non-interventional, observational study is to assess the effect of adalimumab on health-related QoL, work productivity, and healthcare resource utilization (HCRU) in patients with RA in China.

Adalimumab therapy has a well-established and well described safety profile based on extensive post marketing experience and continued clinical trial patient exposure since the first approved indication in 2002 for rheumatoid arthritis. A detailed discussion of the pre-clinical toxicology, metabolism, pharmacology and safety experience with adalimumab can be found in the current Investigator's Brochure. AbbVie is committed to continue to collect safety information including those events that may occur in this trial in order to confirm this established safety profile and to identify any unknown potential adverse reactions, rare events and those events with a long latency. AbbVie is participating in an FDA-requested, TNF inhibitor class wide exploration of the rare appearance of malignancy in subjects/patients who are 30 years of age or younger at the time of diagnosis. The risk of malignancy in this age group has not been established and is difficult to study due to its rarity. AbbVie appreciates your attention to the additional reporting requirements needed in this unlikely event, outlined in Section 11.1.2b under Adverse Event Reporting.

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. 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 Health Assessment Questionnaire Disability Index (HAQ DI) score at week 24 after the initiation of adalimumab. The HAQ DI is selected as the primary point as it is commonly used to assess improvements in physical function in RA clinical trials and recommended by the US Food and Drug Administration (FDA) guidance on RA treatment development (3, 4). In addition, the HAQ-DI has been utilized as a predictor variable in investigations of productivity (5). The HAQ-DI has been demonstrated to be significantly correlated with work-related measures such as work capacity, household work performance, work task performance, and work disability (6-9). In addition, the effect of adalimumab will also be assessed by the secondary outcome measures which are changes to the WPAI, EuroQol 5 dimension (EQ-5D) score, and Short Form 36-Item Health Survey (SF-36) domain scores at weeks 12 and 24 after the initiation of adalimumab in RA. All the analysis will be based on the data as observed.

9.0 Research Methods

9.1 Study Design

This study is designed as a prospective, observational study to assess the effect of adalimumab on health-related QoL and work productivity in patients with RA in China in clinical practice.

The study population will include Chinese adult patients with a diagnosis of RA who meet the requirements per the local label for treatment with adalimumab at the baseline visit. The decision to prescribe adalimumab for RA should be based on clinical practice criteria without taking participation in this study into account. Patients will be included in the study after a physician's decision of initiating Humira.

Approximately 52 patients diagnosed with RA that meet the inclusion and exclusion criteria will be enrolled at approximately 16 sites.

This study is non-interventional and the subjects/investigator will follow the current clinical practice in each site. Not additional task will be required other than current practice to keep the data as "real world data collect".

The observation period for each patient is 24 weeks. All visits are to be scheduled as per routine clinical practice, regardless of study participation. Patients may discontinue adalimumab treatment or the study at any time without prejudice.

The physician will follow the patient during regular clinic visits at intervals as determined by routine clinical practice. Data at the clinic visits within ± 7 days of the study-defined time points will be collected and data at the clinic visits closest to the study-defined time points will be used for statistical analysis (If there are 2 clinic visits equidistant from a study-defined time point which do not correspond to any other visit, data from the EARLIER clinic visit shall be used for the study-defined time point).

The HAQ DI data will be collected at baseline, Week 12 and Week 24 after treatment initiation with adalimumab, as per standard daily clinical practice. In addition, when available, other PROs of work activity and well-being, including the WPAI, EQ-5D, and SF-36, will also be collected.

The HCRU will also be collected, when available. This includes surgical procedures, hospitalizations, bed days in hospital, physician consultations etc. Costs will be assigned based on the HCRU using standardized costs for each participating countries.

Primary Endpoint

- Change in HAQ DI score at week 24 after the initiation of adalimumab, in those patients continuing on adalimumab. This change will be summarized as the mean and 95% confidence interval and will be tested with a paired t-test.

Secondary Endpoint Analysis

- Change in HAQ DI score at week 12 after the initiation of adalimumab, in those patients continuing on adalimumab. This change will be summarized as the mean and 95% confidence interval and will be tested with a paired t-test.
- Change in other patient reported outcomes (SF-36 domain scales, EQ-5D Index, WPAI total lost productivity) at weeks 12 and 24 after the initiation of adalimumab, in those patients continuing on adalimumab. These changes will be summarized as the means and 95% confidence intervals and will be tested with paired t-tests.
- Number and percent of patients achieving a clinically meaningful improvement on the HAQ DI, as defined by a -0.22 point improvement or greater, at weeks 12 and 24 after the initiation of adalimumab, in those patients continuing on adalimumab.

Additional Secondary Endpoint Analysis

- Change in HAQ DI score at week 24 after the initiation of adalimumab, in those patients continuing on adalimumab, compared with those patients not continuing on adalimumab. The mean changes in these two groups will be compared using an independent t-test.
- Healthcare resource utilization will be described using number and percentage within each category (number of consultations, number of procedures received, number of surgeries, number of hospitalizations and length of stay, number of concomitant medications)
- Associations between disease severity and PROs
- Associations between change in disease severity and change in PROs

Exploratory Endpoint Analysis

- Change in patient satisfaction questions at weeks 12 and 24 after the initiation of adalimumab, in those patients continuing on adalimumab. These changes will be summarized as number and percentage of each response and compared with

Kruskal–Wallis test. Satisfaction will also be dichotomized and analysed over time with Cochrane-Armitage test for trends.

- Patient's impression of change at weeks 12 and 24 after the initiation of adalimumab, in those patients continuing on adalimumab (as observed population). These changes will be summarized as number and percentage of each response and compared with Kruskal–Wallis test.

* Note: Patient who misses 2 consecutive adalimumab injections or a total of 3 non-consecutive injections within 24 weeks of treatment will be regarded as "the patient not continuing on adalimumab".

9.1.1 Study Activities

Table 1 Study Activities (Day 1/Baseline Through 6 months)

	Data Collection/Observation	Baseline[a]	Week 12 (V2) ± 7 days	Week 24 (V3) ± 7 days	Early Termination / Drop out	70 days after the Week 24 or the last dose	150 days after the Week 24 or the last dose
Clinician Packet	Inclusion/exclusion form	X					
	Clinical history/patient demographics	X					
	Comorbidities	X					
	DAS28 (ESR) or DAS28 (CRP)	X	X	X	X		
Patient Packet	EuroQoL 5-Dimension (EQ-5D)	X	X	X	X		
	Short Form 36-Item Health Survey (SF-36)	X	X	X	X		
	Health Assessment Questionnaire (HAQ)	X	X	X	X		
	Work Productivity and Activity Impairment Questionnaire (WPAI)	X	X	X	X		
	Healthcare Resource Utilization (HCRU)	X	X	X	X		
	Patient Global Impression of Change (PGIC)		X	X	X		
	Patient Treatment Satisfaction Questions	X	X	X	X		
Clinician Packet	Adverse events (including malignancy)	←				→	
	Pregnancy	←					→

a. The Baseline visit date will serve as the reference for all subsequent visits. A ± 7 day window is permitted around scheduled study visits.

9.2 Setting

The study will take place in China with multiple centers. The study sites will be identified and selected by AbbVie. 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, approximately 52 subjects with clinically diagnosed RA are planned to be enrolled in the study at up to 16 sites.

The recruiting investigators will select potentially eligible patients from consecutive visits within their clinic based on the inclusion and exclusion criteria (Section 9.2.1 and Section 9.2.2). It is the responsibility of each physician to ask every consecutive patient who meets the inclusion criteria of the study to participate to avoid selection bias, and if investigators hold different types of clinics (e.g. routine visit clinics versus emergency clinics), only patients visiting their routine clinics will be used for patient selection. 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:

Patients meeting all of the following inclusion criteria at baseline will be included:

1. Subject has a diagnosis of RA as defined by the 1987 revised ACR classification criteria and/or the ACR/ the European League against Rheumatism (EULAR) 2010 classification criteria (any duration since diagnosis)
2. Male or female subjects ≥18 years of age who is in compliance with eligibility for adalimumab based on the local label
3. Patients with moderate to severe RA defined as DAS28 (ESR) or DAS28 (CRP)>3.2
4. Biologically treatment naïve and initiated adalimumab at baseline visit, as per standard daily clinical practice
5. Availability of clinical data of the previous 12 weeks prior to baseline
6. Ability to self-complete patient questionnaires

7. Patients have signed the authorization (or informed consent where applicable) to disclose and use personal health information after been prescribed with adalimumab.

Additional Inclusion Criteria

8. If female subject, is either not of childbearing potential, defined as postmenopausal for at least 1 year or surgically sterile (bilateral tubal ligation, bilateral oophorectomy and/or hysterectomy) or is of childbearing potential and is practicing an approved method of birth control throughout the study and for 150 days after last dose of study drug.
9. Subject is judged to be in good health as determined by the Principal Investigator based upon the results of medical history, laboratory profile, physical examination, chest x-ray (CXR), and a 12-lead electrocardiogram (ECG) performed during Screening;
10. Subject has a negative TB Screening Assessment. If the subject has evidence of a latent TB infection; the subject must initiate and complete a minimum of 4 weeks of an ongoing TB prophylaxis or have documented completion of a full course of TB prophylaxis, prior to Baseline

9.2.2 Exclusion Criteria:

Patients meeting any of the following exclusion criteria at baseline will be excluded:

1. Patients who are pregnant or breast feeding at enrolment or wish to become pregnant in the next 24 weeks
2. Participation in any RA-related clinical trial at the time of enrolment, at baseline or at any point during the past 24 weeks prior to baseline
3. Patients, who in the clinician's view, may not be able to accurately report their QoL or prior resource utilization
4. Patients, who in the clinician's view, may not be able to adhere to adalimumab therapy over 24 weeks

Additional Exclusion Criteria

5. Subject has been treated with any investigational drug of chemical or biologic nature within a minimum of 30 days or five half-lives (whichever is longer) of the drug prior to the Baseline Visit
6. Prior exposure to biologics that have a potential or known association with PML (i.e., natalizumab (Tysabri®), or rituximab (Rituxan)
7. Positive pregnancy test at Baseline
8. Patients with contraindication or are not appropriate to use adalimumab according to local label or investigators' judgment

9.2.3 Investigator Selection Criteria

Selection of investigators will be made based on qualification by training and experience. AbbVie will provide a list of clinicians that would be able to able to assist in recruiting in a timely manner. AbbVie will contact each clinician to obtain their participation in the study and provide an expected number of patients to be enrolled from that clinic. The ethical review boards recognized by the respective participating sites are required to review and approve the study and patient informed consent.

9.2.4 Study Procedures

The study procedures outlined in Table 1 will be discussed in detail in this section with the exception of adverse events procedures (discussed in Section **Error! Reference source not found.**).

9.2.4.1 Informed Consent

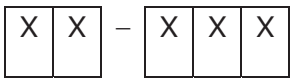
Prior to any study-related data being collected, patient authorization (or informed consent where applicable) will be reviewed, signed and dated by the patient and the person who administered the patient authorization (or informed consent). A copy of the signed patient authorization (or informed consent) will be given to the patient and the original will be placed in the patient's medical record.

9.2.4.2 Patient Assignment

Once the recruiting clinician has obtained the subject's authorization to release medical information and written consent to participate in the study, the clinician will be asked to complete an inclusion and exclusion form (**Error! Reference source not found.**) for patients, thus confirming the patient's eligibility to participate in this study.
Each participating patient will be assigned a 3-digit patient identification number. The numbers should be assigned in sequential, ascending order per site as shown below:

- Site ID; and

- Patient ID: First eligible patient number will be 001, and then the second patient number would be 002



Site ID Patient ID

9.2.4.3 Investigator Recruitment

AbbVie will provide a list of clinicians that would be able to assist in recruiting in a timely manner. AbbViewill contact each clinician to obtain their participation in the study and provide an expected number of patients to be enrolled from that clinic. The ethical review boards recognized by the respective participating sites are required to review and approve the study and patient informed consent.

9.2.4.4 Study site monitoring

AbbVie will closely track enrolment progress for monthly reporting. AbbVie will work closely with the study coordinator at each site to ensure they check the forms when returned from the patients and physicians (e.g., all questions were answered). AbbVie will also be available to answer questions and follow up with the sites if the recruitment process is slow or if there are any errors on the forms. Periodic phone follow-up will be conducted to ensure data collection completeness and quality.

9.2.4.5 Patient Selection

The recruiting investigators will select potentially eligible patients from consecutive visits within their clinic based on the inclusion and exclusion criteria (Section 9.2.1 and Section 9.2.2). It is the responsibility of each physician to ask every consecutive patient who meets the inclusion criteria of the study to participate to avoid selection bias, and if investigators hold different types of clinics (e.g. routine visit clinics versus emergency clinics), only patients visiting their routine clinics will be used for patient selection. The intent is to enroll patients who have been prescribed adalimumab upon the physicians' own discretion.

Medical and Surgical History
A detailed medical history with respect toTB exposure needs to be documented. This information needs to include BCG vaccination, cohabitation with individuals who have had TB, and/or who reside or work in TB endemic locations.

Pregnancy Tests

At the Baseline Visit, subjects of childbearing potential will have a urine pregnancy test performed locally by designated study personnel. If any urine pregnancy test is positive, a

serum pregnancy test will be performed. A lactating or pregnant female will not be eligible for participation or continuation in this study.

All women of childbearing potential will have a repeat urine pregnancy test at the final Study Visit performed locally by designated study personnel.

9.2.4.6 Data Collection

AbbVie will coordinate data collection with each site. At study initiation (Baseline, D0), patients will be asked to provide their written informed consent.

When available, the PRO data as observed will be collected -. The CRF completed by physicians will be returned to the study coordinator/nurse at each site as well.

All data filled in by the patient and physician will be collected by the study coordinator/nurse at each site and returned directly to AbbVie.

All patient and clinician data will be handled preserving confidentiality.

9.2.4.7 Study Documents

Clinical case report form (CRF)

The clinical CRF will document the patient's current status (moderate, severe RA), Disease Activity Score in 28 joints (DAS28), prior and current treatments and other relevant clinical and demographic data to be used in segmenting the population during analysis.

To calculate the DAS28 the physician or specialist nurse will:

1. Count the number of swollen joints (out of the 28)
2. Count the number of tender joints (out of the 28)
3. Take blood to measure the erythrocyte sedimentation rate (ESR) or C reactive protein (CRP); the latest measurement in the medical records may also be used if a blood draw is not standard for that visit
4. Ask the patient to make a 'global assessment of health' which will be indicated by marking a 10 cm line between very good and very bad

The physician or specialist nurse will then mark each component score on the CRF and the DAS28 score if calculated (an online scoring calculator for the DAS28 can be found at http://www.das-score.nl/das28/DAScalculators/dasculators.html).

The DAS28 will be scored using the following formula:

DAS28(CRP) = *0.56 * sqrt(tender28) + 0.28 * sqrt(swollen28) + 0.36 * ln(CRP+1) + 0.014 * (Patient Global assessment of Health in mm)+0.96*

DAS28(ESR) = *0.56 * sqrt(tender28) + 0.28 * sqrt(swollen28) + 0.70 * ln(ESR) + 0.014 * (Patient Global assessment of Health in -mm)*

DAS28 scores will be interpreted using the following categorization:

- Remission: DAS28 ≤ 2.6
- Low Disease activity: 2.6 < DAS28 ≤ 3.2
- Moderate Disease Activity: 3.2 < DAS28 ≤ 5.1
- High Disease Activity: DAS28 >5.1

The full CRF is presented in **Error! Reference source not found.**.

PRO questionnaires

The following PRO questionnaires will be included in the patient questionnaire packet.

Health Assessment Questionnaire Disability Index (HAQ DI)

The HAQ DI is a patient-reported questionnaire to assess functioning impacted by RA. It includes the categories of dressing and grooming, arising, eating, walking, hygiene, reach, grip and common daily activities. It asks patients about the amount of difficulty they experience in these activities as well as the use of aids and/or devices. The HAQ also has a numeric rating scale (NRS) (13) to assess pain on a scale from 0 to 10. Self-administered by the patient, the completion time is approximately 3-4 minutes. The full version of HAQ DI is presented in **Error! Reference source not found.**.

Short Form (36) Health Survey (SF-36)

The SF-36 is a patient-reported questionnaire of patient health-related QoL. It measures generic health concepts relevant across age, disease, and treatment groups. There are 36 items in total and the recall period is the last 4 weeks. The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale. Completion time for the SF-36 is approximately

10 minutes. The full version of SF-36 is presented in **Error! Reference source not found.**.

EuroQol 5 dimension, 3 level quality of life questionnaire (EQ-5D-3L)

The EQ-5D-3L measures the patient's overall health state in a descriptive system of health-related QoL states consisting of five dimensions (mobility, self-care, usual activities, pain/discomfort, and anxiety/depression) each of which can take one of three responses. The responses record three levels of severity ('no problems', 'some problems', and 'extreme problems) within a particular EQ-5D-3L dimension (14, 15). In addition, a VAS rates current health state between 0-100. The EQ-5D-3L results can be converted to health utility scores. Completion time for the EQ-5D-3L is approximately 2-3 minutes. The full version of EQ-5D-3L is presented in **Error! Reference source not found.**.

Work Productivity and Activity Impairment (WPAI)

The WPAI is a patient-reported questionnaire to measure work and activity impairment during the past seven days. It determines employment status, hours missed from work due to the disease (i.e. RA), hours missed from work for other reasons, hours actually worked, the degree to which the disease affected work productivity while at work and the degree to which the disease affected activities outside of work. Additional questions around employment status will be incorporated into the survey. The completion time for the WPAI is approximately 2-5 minutes. The full version of WPAI is presented in **Error! Reference source not found.**.

All of the above questionnaires will be used with the validated Chinese version.

Patient Global Impression of Change (PGIC)

The PGIC measures the patient's perceptions of changes in their disease. It consists of one question asking about the change in their condition; for this study, the base will be "since you initiated your adalimumab treatment". The completion time for the PGIC is less than 1 minute. The full version of PGIC is presented in **Error! Reference source not found.**.

Patient Treatment Satisfaction Questions

The patient treatment satisfaction questions were developed de novo for this study and are not considered "validated" questions. Self-administered by the patient, the completion time for the patient treatment satisfaction questions is approximately 1-2 minutes. The full version of patient treatment satisfaction questions are presented in **Error! Reference source not found.**I.

Healthcare Resource Utilization (HCRU) Questionnaire

The HCRU questionnaire will collect data on the healthcare resources consumed in the prior 3 months, as recall beyond 3 months may be problematic in an older population (16). HCRU collection will include data such as the number of physician visits and to which physician (GP, specialist), Emergency Department visits, hospitalizations, and other drugs as well as devices and aids purchased to assist in their mobility due to RA. The HCRU questionnaire will be part of the patient questionnaire and will be distributed to patients together with the PRO questionnaires (Appendix D to Appendix I). The full HCRU questionnaire is presented in **Error! Reference source not found.**J and will be used with the validated Chinese version.

9.2.5 Adverse Events

Adverse events, whether in response to a query, observed by site personnel, or reported spontaneously by the subject will be recorded. Adverse events definition and serious adverse event categories are described in detail in Section 11.0.

9.2.6 Removal of Subjects from Therapy or Assessment

1. **Discontinuation of Individual Subjects**

A subject may withdraw from the study at any time. The Investigator may discontinue any subject's participation for any reason, including an adverse event, safety concerns or failure to comply with the protocol.

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

- Clinically significant abnormal laboratory result(s) or adverse event(s), as determined by the Investigator in consultation with the AbbVie Medical Monitor.
- The Investigator believes it is in the best interest of the subject.
- The subject requests withdrawal from the study.
- Inclusion and exclusion criteria violation was noted after the subject started study drug, when continuation of the study drug would place the subject at risk as determined by the AbbVie Medical Monitor (see *Section 5.2 and Section 7.0*).

- Introduction of prohibited medications or dosages when continuation of the study drug would place the subject at risk as determined by the AbbVie Medical Monitor.
- Subject is non-compliant with TB prophylaxis.
- The subject becomes pregnant while on study medication.
- Subject has dysplasia of the gastrointestinal tract or a malignancy, except for localized non-melanoma skin cancer. Discontinuation for carcinoma in-situ of the cervix is at the discretion of the Investigator.
- Subject is diagnosed with lupus-like syndrome, multiple sclerosis or demyelinating disease.
- Subject is significantly non-compliant with study procedures which would put the subject at risk for continued participation in the trial, as determined by the Investigator, in consultation with the AbbVie Medical Monitor.

Following discontinuation of the study drug, the subject will be treated in accordance with the Investigator's best clinical judgment. A final phone call will be made to the subject approximately 70 days after the last dose of study drug to determine the status of any ongoing AEs/SAEs or the occurrence of any new AEs/SAEs.

For subjects that are considered lost to follow-up, reasonable attempts should be made to obtain information on the final status of the subject.

9.3 Variables

Variables:
Primary Variable

- Change in HAQ DI score at week 24 from the baseline

Secondary Variable

- Change in HAQ DI score at week 12 from the baseline
- Change in other PROs (SF-36 domain scales, EQ-5D Index, Work Productivity and Activity Impairment Questionnaire [WPAI]) from baseline to weeks 12 and 24

- Number and percent of patients achieving a clinically meaningful improvement on the HAQ DI, from baseline to weeks 12 and 24

Additional Secondary Variable

- Change in HAQ DI score from baseline to week 24
- Changes in the disease severity and PROs from baseline to week 24
- Healthcare Resource Utilization (HCRU) at baseline, weeks 12 and 24

Exploratory Variable

- Change in patient satisfaction questions from baseline to weeks 12 and 24
- Patient's impression of change at weeks 12 and 24 from baseline

9.4 Data Sources

Case Report Forms (CRFs) and patient questionnaires.

Collection of data includes but not limited to subject demographics, clinical history, comorbidities, spontaneous adverse events, and concomitant medications. The following questionnaires will be utilized to collect data directly from participating subjects:

- EQ-5D
- SF-36
- HAQ DI
- WPAI
- HCRU
- Patient Global Impression of Change (PGIC)
- Patient Treatment Satisfaction Questions

9.5 Study Size

Approximately 52 patients diagnosed with RA will be recruited. The planned sample size provides 80% power for detecting a statistically significant improvement in HAQ-DI (Δ HAQ-DI < 0) assuming a mean ΔHAQ-DI of -0.21 and a standard deviation of 0.5 (reference 11), at two-sided significance level of 0.05 and accounting for a 10% dropout rate. The sample size also provides 99% power for detecting a statistically significant clinically meaningful improvement in HAQ-DI (ΔHAQ-DI < -0.22) assuming a mean Δ HAQ-DI of -0.5 and a standard deviation of 0.7, at two-sided significance level of 0.05 and accounting for a 10% dropout rate.

9.6 Data Management and Storage Process

9.6.1 Data Management

Data management and data quality check will be performed to remove errors and inconsistencies in order to assure the appropriateness of the study data set to assess the study objectives. Data entry screens will be developed and tested prior to initiating data collection to reduce data entry errors. If required, IMS will provide AbbVie with data for analysis.

Each site coordinator will be instructed to answer patients' queries which may arise in relation to the questionnaires and check the patients' input to make sure all questions are answered.

9.6.2 Storage Process

Following data quality checks, each dataset will be converted to SAS and merged for analysis. All information included in the CRF and the patients' questionnaires will be checked in order to detect possible queries to solve and will be extracted to a specifically designed database, where it will be validated by IMS personnel to ensure its quality. Finally, data analysis will be conducted and final results reported.

The databases will be stored in IMS data servers. Data servers are submitted to daily backups in order to increase the security on all data managed in the collection process.

All paper based questionnaires will be stored in a secured, locked area for a period of seven (7) years, after which all data will be shred using an agency specialized in disposal of confidential documents.

9.7 Data Analysis

9.7.1 Statistical and Analytic plans

A statistical analysis plan (SAP) will be developed describing the specific analysis that will be performed including, and in addition to, the analysis described here. All analysis will be performed in accordance with the approved analysis plan. The following provides an overview of some of the analysis.

The scoring of the PRO questionnaires will be done in accordance to the developers' recommendations.

A separate statistical analysis plan will be developed describing the specific analysis that will be performed including and in addition to the analysis described here.

9.7.2 Analyzable population

All subjects who received at least one dose of adalimumab during the study will be included. The main analysis will be conducted on the pooled population, where appropriate, with each individual country analyzed separately as supportive data.

9.7.3 Planned Methods of Statistical Analysis

All statistical tests will be two-tailed with a significance level of 0.05. Descriptive statistics will be provided. Descriptive analysis will be conducted on all key parameters and presented as mean, standard deviation, minimum, maximum, and median when continuous and as "n" and percent when categorical. Change from adalimumab initiation to 24 weeks will be calculated and evaluated for significant improvements using paired t-tests / ANOVA for parametric and Wilcoxon signed-rank for non-parametric data. Analysis will be also be conducted by severity level (moderate vs severe), disease duration quartile (to compare to prior work) and up to two (2) other subgroups. Cochran-Armitage test of trends or other similar methods may be used to compare categories of subjects.

9.7.4 Primary Endpoint Analysis

The primary endpoint variable will be the change in HAQ DI score at week 24 after the initiation of adalimumab, in those patients continuing on adalimumab.

The objective of the primary endpoint analysis will be to demonstrate that treatment with adalimumab improves functioning as measured by the HAQ DI in subjects with RA following treatment initiation. This change will be summarized as the mean and 95% confidence interval and will be tested with a paired t-test.

The primary analysis will be summarized as the mean and 95% confidence interval and will be tested with a paired t-test without adjusting for baseline disease severity. For sensitivity analysis, the mean change in HAQ DI at week 24 will be analyzed using ANOVA adjusting for baseline disease severity.

9.7.5 Secondary Endpoint Analysis

The main secondary endpoint variable will be the change in HAQ DI at week 12 after the initiation of adalimumab.

The objective of endpoint analysis will be to demonstrate that treatment with adalimumab improves functioning as measured by HAQ DI in subjects with RA compared to baseline.

The main secondary analysis will be summarized as the mean and 95% confidence interval and will be tested with a paired t-test without adjusting for baseline disease severity. For sensitivity analysis, the mean change in HAQ DI at week 12 will be analyzed using ANOVA adjusting for baseline disease severity.

Other secondary analysis include:

- Change in other patient reported outcomes (SF-36 domain scales, EQ-5D Index, WPAI total lost productivity) at weeks 12 and 24 after the initiation of adalimumab, in those patients continuing on adalimumab. These changes will be summarized as the means and 95% confidence intervals and will be tested with paired t-tests.
- Number and percent of patients achieving a clinically meaningful improvement on the HAQ DI, as defined by a -0.22 point improvement or greater, at weeks 12 and 24 after the initiation of adalimumab, in those patients continuing on adalimumab.

9.7.6 Additional Secondary Endpoint Analysis

Additional efficacy analysis include:

- Change in HAQ DI score at 24 weeks after the initiation of adalimumab, in those patients continuing on adalimumab, compared with those patients not continuing on adalimumab. The mean changes in these two groups will be compared using an independent t-test.
- Healthcare resource utilization will be described using number and percentage within each category (number of consultations, number of procedures received, number of surgeries, number of hospitalizations and length of stay, number of concomitant medications)
- Associations between disease severity and PROs
- Associations between change in disease severity and change in PROs

9.7.7 Exploratory Endpoint Analysis

- Change in patient satisfaction questions at weeks 12 and 24 after the initiation of adalimumab, in those patients continuing on adalimumab. These changes will be summarized as number and percentage of each response and compared with Kruskal–Wallis test. Satisfaction will also be dichotomized and analyzed over time with Cochrane-Armitage test for trends.
- Patient's impression of change at weeks 12 and 24 after the initiation of adalimumab, in those patients continuing on adalimumab (as observed population). These changes will be summarized as number and percentage of each response and compared with Kruskal–Wallis test.

9.7.8 Safety Analysis

Adverse events occurring while participants are on adalimumab will be coded using Common Terminology Criteria for Adverse Events (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 summarized.

9.7.9 Additional Analysis

Additional analysis 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 analysis will specifically test for differential changes across the subgroups defined by the potential modifiers using general linear models.

9.7.10 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 24 weeks who remain on adalimumab. Item level data on the PROs will be imputed according to the developers' recommendations. There will be no other imputation for missing data.

9.8 Quality Control

9.8.1 Ethics and Quality

Prior to any study-related data being collected, informed consent form will be reviewed, signed and dated by the patient and the person who administered the informed consent. A copy of the signed informed consent will be given to the patient and the original will be placed in the patient's medical record.

9.8.2 Quality Assurance

Prior to the initiation of the study, physician and site personnel will be trained on the study. Training will include a detailed discussion of the protocol, performance of study procedures, and completion of the CRFs and paper questionnaires.

All sites will be monitored during the course of study participation. One hundred percent (100%) source document review for safety will be performed.

All clinical data will be documented via the CRF. Study coordinators at each site will check the paper CRFs completed by the physicians and questionnaires completed by patients (e.g., all questions were answered). Data entry will be conducted by IMS. After entry of the data, computer logic checks will be run to check for inconsistent data. Any necessary corrections will be made to the database and documented via addenda, queries, and source data clarification forms.

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, 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 patient questionnaires for accuracy and completeness 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.

Protocol Deviation

For the purposes of this protocol, reportable deviations are defined as:

- Subject entered into the study even though she/he did not satisfy entry criteria
- Subject who developed withdrawal criteria during the study and was not withdrawn
- Subject who received wrong treatment
- Subject who received excluded or prohibited concomitant treatment

9.9 Limitations of the Research Methods

The study is to be performed as a non-interventional study. Unlike clinical studies, obtainable data are limited and there is a possibility of missing data.

9.10 Other Aspects

9.10.1 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.

9.10.2 Training Log

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

9.10.3 Visitor Log

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

9.10.4 Responsibilities of the Principal Investigator

The Principal Investigator is responsible for oversight of enrolment, 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.

9.10.5 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.

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

Death of Patient:	An event that results in the death of a patient.
Life-Threatening:	An event that, in the opinion of the investigator, would have resulted in immediate fatality if medical intervention had not been taken. This does not include an event that would have been fatal if it had occurred in a more severe form.
Hospitalization:	An event that results in an admission to the hospital for any length of time. This does not include an emergency room visit or admission to an outpatient facility.
Prolongation of Hospitalization:	An event that occurs while the study patient is hospitalized and prolongs the patient's hospital stay.
Congenital Anomaly:	An anomaly detected at or after birth, or any anomaly that results in fetal loss.
Persistent or Significant Disability/Incapacity:	An event that results in a condition that substantially interferes with the activities of daily living of a study 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).
Important Medical Event Requiring Medical or Surgical Intervention to Prevent Serious Outcome:	An important medical event that may not be immediately life-threatening or result in death or hospitalization, but based on medical judgment may jeopardize the 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.

Mild:	The adverse event is transient and easily tolerated by the patient.
Moderate:	The adverse event causes the patient discomfort and interrupts the patient's usual activities.
Severe:	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:

Reasonable Possibility	An adverse event where there is evidence to suggest a causal relationship between the product and the adverse event.
No Reasonable Possibility	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 70 days following the intake of the last dose of adalimumab taken during the study.

11.5 Serious Adverse Event Reporting

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

- For events from patients using an AbbVie product - notify the AbbVie Emergency contact person (ASR) identified at the beginning of the protocol within 24 hours of the physician becoming aware of the event.

11.6 Pregnancy Reporting

Pregnancies in patients will be collected from the date of the first dose through 150 days following the last dose of adalimumab taken during the study. In the event of a pregnancy occurrence in the patient, the physician will notify AbbVie Emergency contact person identified in protocol section 3.0 within 24 hours of the physician becoming aware of the pregnancy.
Information regarding a pregnancy occurrence in a study subject and the outcome of the pregnancy will be collected.

This protocol requires all SAEs and AESIs as outlined in protocol section 11.1 to be actively solicited. The safety profile of adalimumab which has over 3.5 million patient years of post-marketing exposure is stable and well established; non-serious events will not be actively solicited as these events are not likely to contribute to the further

understanding of the safety profile of the product. Any non-serious AEs will be collected as spontaneous reports if AbbVie is notified.

11.7 Malignancy 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 physician will notify the AbbVie contact person identified in protocol section 3.0 within 24 hours of the physician becoming aware of the event.

Adalimumab therapy has a well-established and well described safety profile based on extensive postmarketing experience and continued clinical trial patient exposure since the first approved indication in 2002 for rheumatoid arthritis. A detailed discussion of the pre-clinical toxicology, metabolism, pharmacology and safety experience with adalimumab can be found in the current Investigator's Brochure. AbbVie is committed to continue to collect safety information including those events that may occur in this trial in order to confirm this established safety profile and to identify any unknown potential adverse reactions, rare events and those events with a long latency. AbbVie is participating in an FDA-requested, TNF inhibitor class wide exploration of the rare appearance of malignancy in subjects/patients who are 30 years of age or younger at the time of diagnosis. The risk of malignancy in this age group has not been established and is difficult to study due to its rarity. AbbVie appreciates your attention to the additional reporting requirements needed in this unlikely event, outlined in Section 11.7 under Malignancy Reporting.

11.8 Product Complaint

A Product Complaint is any Complaint related to the biologic or drug component of the product or to the medical device component(s).

For a product this may include, but is not limited to, damaged/broken product or packaging, product appearance whose color/markings do not match the labeling, labeling

discrepancies/inadequacies in the labeling/instructions (example: printing illegible), missing components/product, device not working properly, or packaging issues.

For medical devices, a product complaint also includes all deaths of a patient using the device, any illness, injury, or adverse event in the proximity of the device, an adverse event that could be a result of using the device, any event needing medical or surgical intervention including hospitalization while using the device and use errors.

Any information available to help in the determination of causality by the device to the events outlined directly above should be captured.

12.0 Plans for Disseminating and Communicating Study Results

At the end of this observational study, a report will be written by AbbVie or a CRO working on behalf of AbbVie. The required standard study report template will be followed. This report will contain a description of the objectives of the study, the methodology and its results and conclusions. The completed CRFs, [patient questionnaires, interim assessments], the final study output and study report are the confidential property of AbbVie and may not be released to unauthorized people in any form (publications or presentations) without express written approval from AbbVie. The study results will be submitted to local authorities per local laws and regulations.

The results of this PMOS may be published by AbbVie or by any one of the participating investigators after agreement with AbbVie.

12.1 Ethical and Legal Consideration

All participant data will be handled in a manner compliant with all local regulatory and privacy laws. All parties will ensure protection of subject personal data and will not include subject names on any sponsor forms, reports, publications, or in any other disclosures, except where required by law. Appropriate role-based access to minimum necessary information will be maintained so that only authorized individuals have access to protected health information (PHI).

Abbvie shall comply with all applicable laws regarding the reporting of spontaneous adverse events (AEs) to the relevant local authorities in China-. Abbvie will follow the International Conference on Harmonization of Good Clinical Practice (ICH-GCP)

guidelines for AE reporting and report all spontaneously reported AEs within the required timeframe (usually within 24 hours of discovery).

All staff working directly with patient data and/or having direct contact with healthcare practitioners will have received formal training to ensure they have a clear understanding of how to recognize an AE and inform Affiliate Safety Specialist so that they are in full compliance with local laws regarding AE reporting.

The study will be reviewed and approved by the appropriate Ethics Committee(s) at each site prior to the start of patient recruitment, according to the specific legal requirements in each country.

12.2 Confidentiality

12.2.1 Patient confidentiality

Information on patients' identity shall be considered as confidential for all effects and purposes. Each site and patient will have a code in the study. Sites will be automatically coded by AbbVie. Patients will be assigned a sequential number by the site coordinator upon meeting all inclusion and no exclusion criteria.

The patients' identity should not be revealed nor published under any circumstances. Patient data recorded in the CRF will be documented anonymously, coded with a patient number in such a way that only the investigator and site staff may associate particular data with an identified or identifiable individual or his/her medical record. All other parties involved in data management, analysis and storage will receive, and subsequently analyze, non-identifiable patient data.

12.2.2 Data confidentiality

By signing the investigator's confidentiality agreement, the investigator affirms to AbbVie/IMS that information furnished by AbbVie/IMS to the investigator will be kept in confidence and such information will be divulged to any expert committee, affiliated institution, and employees only under an appropriate understanding of confidentiality with such committee, affiliated institution and employees.

12.3 Study administration

The entire study will be managed by a project coordinator at AbbVie who will coordinate the project and maintain fluid communication with the study sponsor, the study team and the director at AbbVie.

As part of the monitoring plan, regular phone calls (at least every two weeks) will be made between AbbVie and local site coordinator in order to check inclusion status, resolve any issues, check data plausibility, etc.

12.4 Investigators compliance

By signing the investigator's agreement, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol, generally accepted standards of good clinical practice and all applicable laws, rules and regulations relating to the conduct of the study.

The investigator shall prepare and maintain complete and accurate study documentation in compliance with applicable national and local laws, rules and regulations and, for each patient participating in the study, promptly record all data in the CRF as required by this protocol.

12.5 Risks, Insurance, Indemnity and compensation

This is a non-interventional observational study. It does not involve any direct patient intervention with respect to laboratory tests, examinations or drug treatment.

The Sponsor will provide Product Liability insurance for all subjects included in the study.

12.6 Discontinuation or Drop-out

Patients' participation in the study is completely voluntary, and they are allowed to withdraw or discontinue from the study. The following three situations will be counted as study drop-out:

1) Patient is switched off Adalimumab
2) Patient is not willing to continue participation in the study
3) Patient disappears and cannot be contacted anymore

For the first two situations, the Early Termination Form (**Error! Reference source not found.**) will be provided for the patients and their physicians to fill in.

Patients not completing questionnaires will not be classified as drop-out. For example, if a patient missed Week 12 questionnaires for some reason, he/she can still fill in Week 24 questionnaires.

12.7 Quality control and audit

Steps to be taken to ensure the accuracy and reliability of data include the selection of qualified investigators and appropriate study centers, 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 patient 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.

The study will be performed following AbbVie Standard Operating Procedures (SOPs) for Observational Studies.

13.0 References

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AbbVie Inc. (AbbVie)

Post Marketing Observational Study

Protocol

Real-World Outcome of Adalimumab on Rheumatoid Arthritis Patients in China

Approved by:

Name	Date
[redacted] Study Designated Physician	
/ /	
Name [redacted]	Date
Name [redacted]	Date
Name [redacted]	Date
Name [redacted]	Date