Study information

Title	Defining which remission criterion at Month 6 predicts remission at Month 12 in a real life clinical practice, in a cohort of rheumatoid arthritis patients treated with etanercept (Enbrel®)
Protocol number	B1801378
Protocol version identifier	Amendment 2
Date of last version of protocol	26 January 2015
Active substance	Tumor necrosis factor alpha (TNF-α) inhibitors (L04AB01): Etanercept
Medicinal product	Enbrel®
Research question and objectives	This study aims both to evaluate rheumatoid arthritis remission according to different criteria and to look at which remission criterion at Month 6 is the most predictive for remission at Month 12.
Author	PPD , PhD PPD Belgium

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1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACR	American College of Rheumatology
AE	Adverse Event
AEM	Adverse Event Monitoring
CDAI	Clinical Disease Activity Index
CRP	C-Reactive Protein
DAS28	Disease Activity Score-28
DCP	Data Collection Point
eCRF	electronic Case Report Form
EDP	Exposure During Pregnancy
EULAR	European League Against Rheumatism
GSUS	Grey-scale Ultrasonography
HAQ	Health Assessment Questionnaire
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MKUS	Musculoskeletal Ultrasonography
NIS	Non-Interventional Study
PDUS	Power Doppler Ultrasonography
PtGA	Patient Global Assessment of disease
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SDAI	Simplified Disease Activity Index
SJC	Swollen Joint Count
SmPC	Summary of Product Characteristics
TJC	Tender Joint count
TNF-alpha	Tumor Necrosis Factor Alpha
US	Ultrasound
US7	Seven-joint ultrasound

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation	Address
PPD , MD	Principal Investigator	Rheumatologist	PPD Belgium
PPD , MD	Principal Investigator	Rheumatologist	PPD Belgium

Responsible for input in protocol

Name, degree(s)	Title	Affiliation	Address
PPD , PharmD	Medical Advisor/Clinical Lead	Pfizer sa/nv	PPD Belgium
PPD	eCRF/ePlatform vendor General Manager	Lambda Plus sa/nv	PPD Belgium
PPD , PhD	PPD of Medical Writing, Data Management and Biostatistics	ECSOR sa/nv	PPD Belgium

3. AMENDMENTS AND UPDATES

On January 26, 2015, the recruitment status was as follows: 34 patients included in the cohort 1st biological versus 4 in the cohort 2nd biological.

For our predictive model, we need 100 evaluable patients but the cohort in which the patients are recruited will not impact the results.

In order to have 100 evaluable patients for the predictive model and given the above mentioned recruitment status, we decided to amend the protocol to allow the needed number of patients to be recruited in whichever cohort: 1st or 2nd. This will limit the potential extension of the recruitment period. .

4. MILESTONES

Milestone	Planned date
Completion of feasibility assessment	30 June 2014
Start of data collection	15 July 2014
End of data collection	30 June 2016
Interim report 1	30 January 2017
Final study report	31 May 2017

5. RATIONALE AND BACKGROUND

Today, both in clinical studies and clinical practice the Disease Activity Score-28 (DAS28) is the golden standard for measuring disease activity in rheumatoid arthritis (RA).

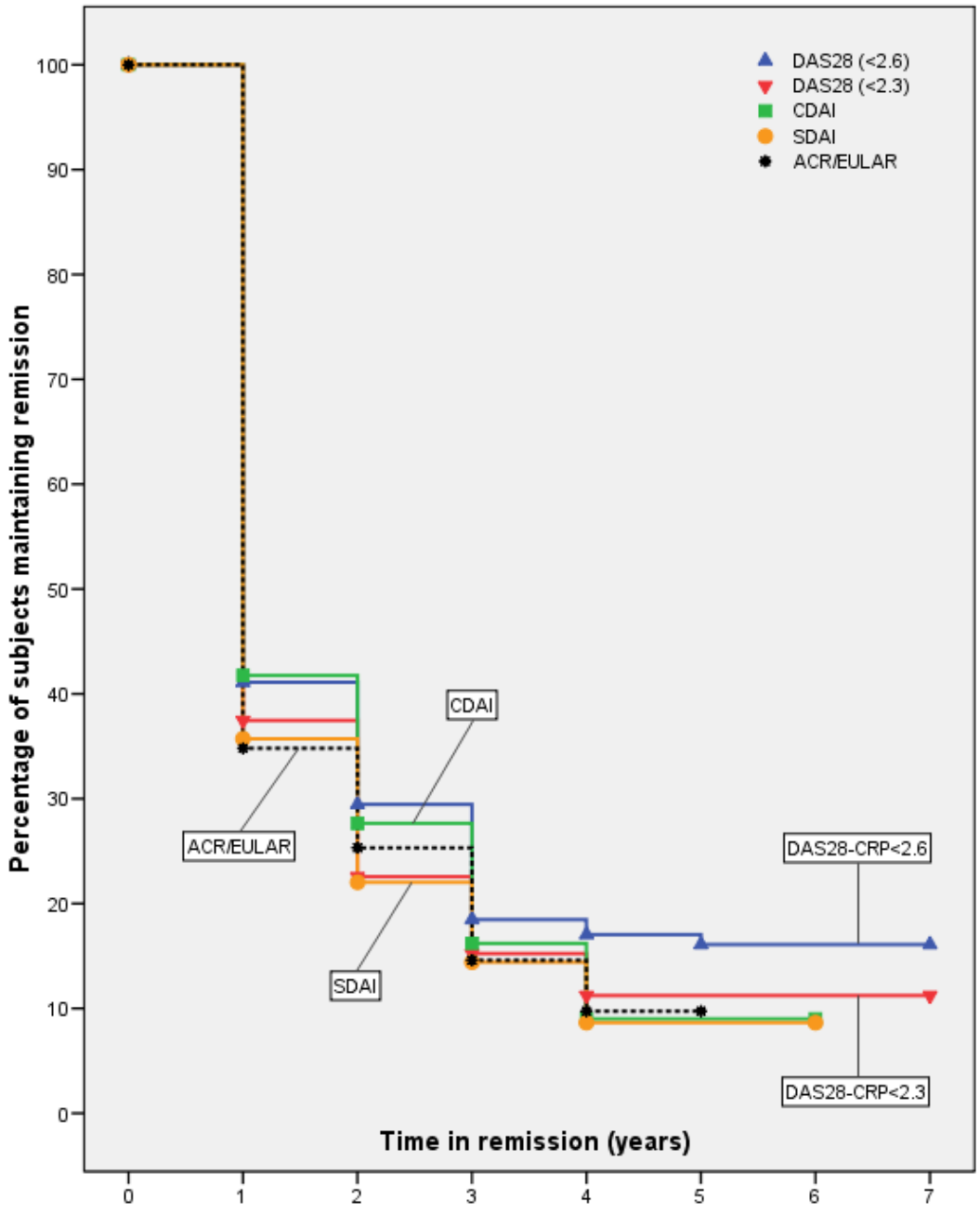
In the 2013 guidelines from the European League Against Rheumatism (EULAR) for the management of RA, recommendation 2 clearly states: "Treatment should be aimed at reaching a target of remission or low disease activity in every patient."

This same article mentions that remission as defined by the DAS28 <2.6 is not regarded as sufficiently stringent to define remission, referring to the 2011 EULAR/American College of Rheumatology (ACR) remission criteria (Figure 1):

- Clinical Practice: the Boolean definition (SJC<1, TJC<1 and PtGA<1) and CDAI ≤ 2.8 (SJC= Swollen Joint Count, TJC= Tender Joint Count, PtGA= Patient Global Assessment of disease, CDAI= Clinical Disease Activity Index)

- Clinical Studies: the Boolean definition (SJC<1, TJC<1 and PtGA<1, CRP <1) and SDAI ≤ 3.3 (CRP= C-Reactive Protein, SDAI= Simplified Disease Activity Index)

Figure 1. Percentage of subjects maintaining remission as a function of time and criteria (Prince et al., 2012)



Only one study has evaluated these new criteria in a real life clinical practice. The article by Prince et al. (year and reference at the end of the protocol) concludes that in an RA population, only a minority of patients is in sustained remission. Further evaluation of these criteria in observational studies is needed.

Musculoskeletal ultrasonography (MKUS) has emerged as a tool with the potential to enhance disease assessment and management in this area. This includes applications in patients with undifferentiated arthropathy attending an early inflammatory arthritis clinic, in which the diagnosis of inflammatory disease may be confirmed or refuted at an early stage, and those with treated RA where accurate measurement of outcomes, such as response to therapy, structural damage and disease remission, are extremely important. This imaging modality is safe and portable, making it ideal for outpatient and inpatient settings, and can be used to assess many joints in multiple planes and to demonstrate changes in disease activity and structural damage over time. US is gaining popularity among rheumatologists, as increasing evidence supports the added value of a physician-performed ultrasonography assessment above traditional clinical, laboratory and radiographic measures, enabling greater confidence in diagnostic and management decisions (Brown, 2009, Dougados et al., 2010; Iagnocco et al., 2008). Remission when defined by clinical remission criteria (DAS, simplified disease activity index, etc…) does not always equate to the complete absence of inflammation as measured by US (Wakefield et al., 2012).

The new seven-joint ultrasound (US7) score was proposed by Backhaus et al. (2009). This is the first MKUS composite scoring system, combining soft tissue lesions (synovitis and tenosynovitis/paratenonitis) and destructive processes (erosions) in a single scoring system. The US7 score includes MKUS examination of the following joints of the clinically more affected side: wrist, MCP II and III, PIP II and III, MTP II and V. The joints are examined by Grey-Scale Ultrasonography (GSUS) and Power Doppler Ultrasonography (PDUS) for synovitis and tenosynovitis/paratenonitis from a dorsal and palmar/plantar aspect, and for erosions from a dorsal, palmar/plantar and radial/lateral (only MCP II and MTP V) aspect. Synovitis in GSUS is analysed semiquantitatively (0–3) according to Scheel et al. (2005): 0: absence; 1: small hypoechoic/anechoic line beneath the joint capsule (mild synovitis); 2: elevation of the joint capsule parallel to the joint area (moderate synovitis); 3: strong distension of the joint capsule (severe synovitis) (see Figure 2and Figure 3).

Figure 2. Semi-quantitative (grade 0-3) grey-scale ultrasound synovitis score at the wrist joint in the dorsomedian longitudinal axis

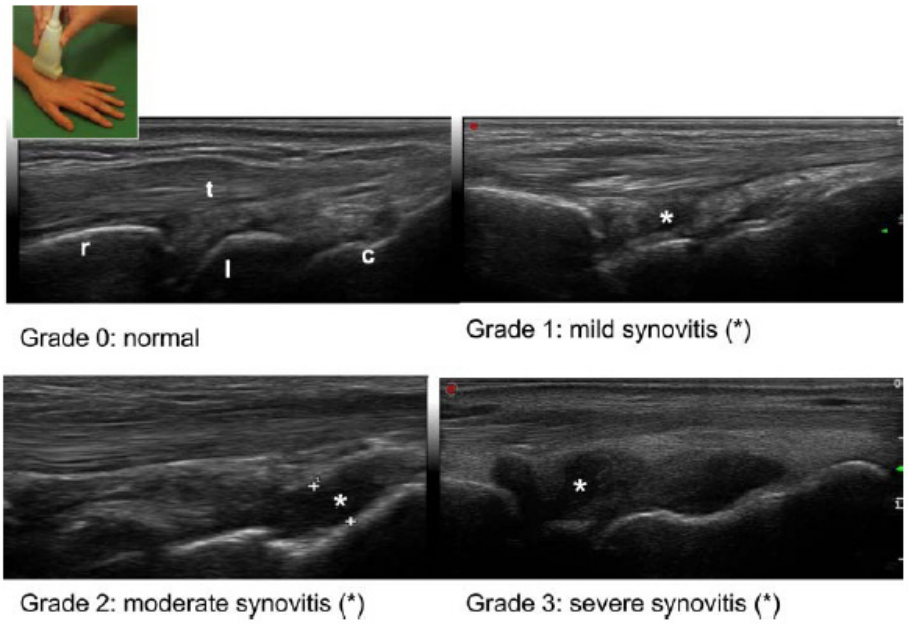


Figure 1 Semi-quantitative (grade 0–3) grey-scale ultrasound synovitis score at the wrist joint in the dorsomedian longitudinal axis.

Figure 3. Semiquantative (grade 0-3) grey-scale ultrasound synovitis score at the metacarpophalangeal II/III joints in the palmar longitudinal axis

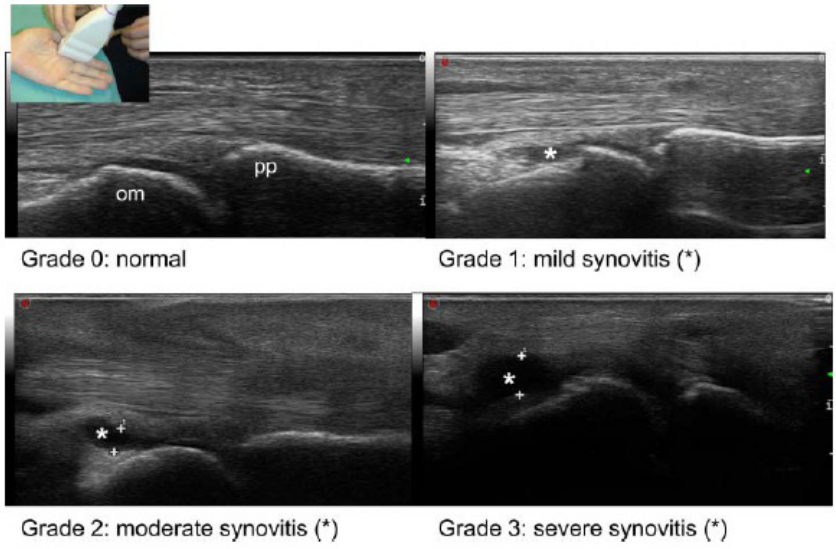


Figure 3 Semiquantitative (grade 0–3) grey-scale ultrasound synovitis score at the metacarpophalangeal II/III joints in the palmar longitudinal axis.

The PDUS evaluation for synovitis (see Figure 4 and Figure 5) and tenosynovitis/paratenonitis is scored according to the scoring system of Szkudlarek et al. (2003).
Tenosynovitis/paratenonitis and erosions in GSUS are registered on a binary basis (0/1).

Figure 4. Semiquantitative (grade 0-3) power Doppler ultrasonography synovitis score at the wrist joint in the dorsomedian longitudinal axis

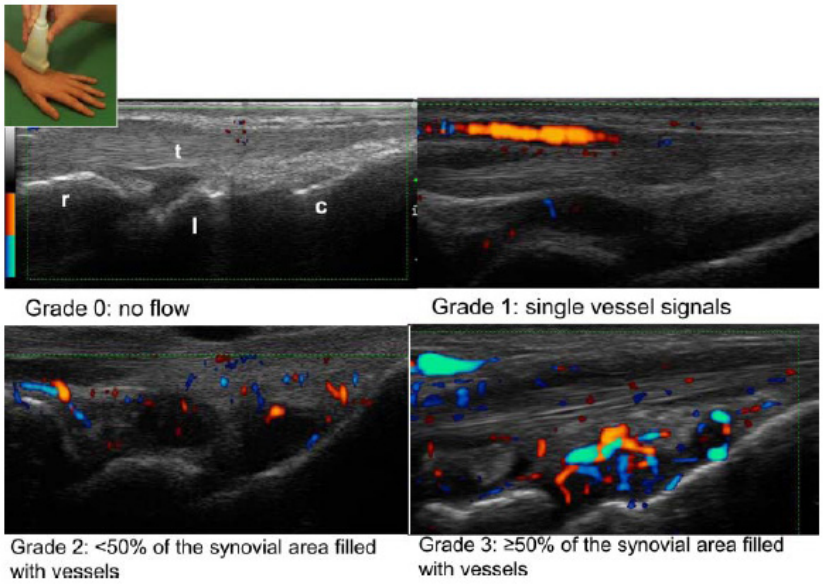


Figure 2 Semiquantitative (grade 0–3) power Doppler ultrasonography synovitis score at the wrist joint in the dorsomedian longitudinal axis.

Figure 5. Semiquantitative (grade 0-3) power Doppler ultrasonography synovitis score at the metacarpophalangeal II/III joints in the dorsal longitudinal axis

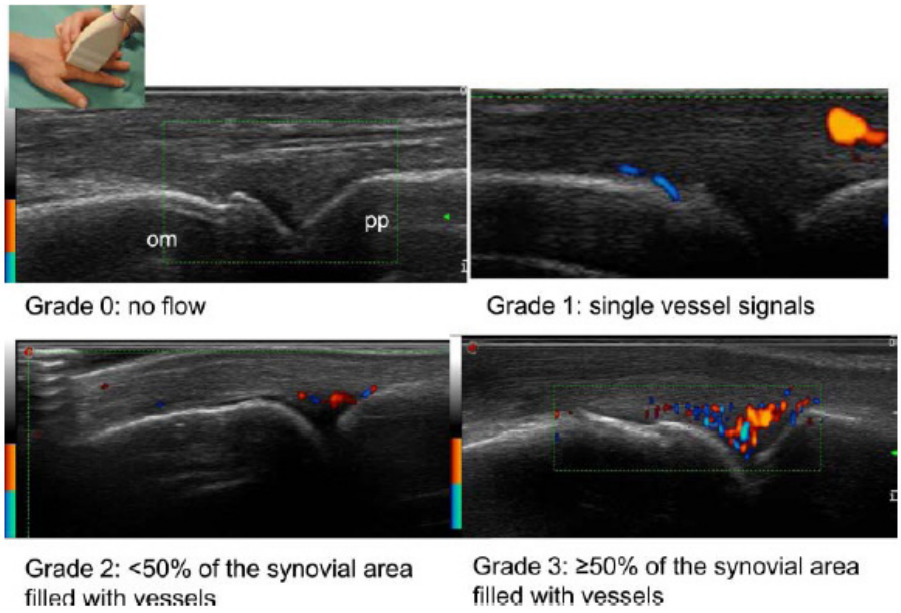


Figure 4 Semiquantitative (grade 0–3) power Doppler ultrasonography synovitis score at the metacarpophalangeal II/III joints in the dorsal longitudinal axis.

A recently published US7 reliability study investigated the inter-observer and intra-observer reliability of sonographers, determining the US7 score under conditions similar to those of daily rheumatological practice. The median overall κ value for detecting synovitis was κ=0.51, for tenosynovitis/paratenonitis κ=0.57 and for erosions κ=0.45. This study also showed that the US7 score has the potential also in multicentre analysis to assess structural changes with moderate to good reliability (Ohrndorf et al. 2012).

In today's clinical practice, there is still an existing need to define which remission criterion can best be used to predict remission in the long run.

There is a tendency to link (sustained) remission with a dose down strategy. However, dose down often results in flaring of the disease and flare rates go as high as 70% in this dose down population, expressing an urgent need for better defining the pool of patients in which dose down could be an option to consider.

6. RESEARCH QUESTION AND OBJECTIVES

This study aims both to evaluate remission according to different criteria and to look at which remission criterion at Month 6 is the most predictive for remission at Month 12.

6.1. Primary Objective

To determine which remission criterion at Month 6 predicts remission at Month 12 the best.

6.2. Secondary Objectives

- Describe the percentage of patients in remission at the different DCPs (Data Collection Points) according to different remission criteria: CDAI, SDAI, DAS28, DAS28 in combination with Ultrasound, EULAR Boolean definition for clinical practice and clinical studies.

- Describe percentage of the same patients in remission at the different DCPs, according to different remission criteria: CDAI, SDAI, DAS28, DAS28 in combination with Ultrasound, EULAR Boolean definition for clinical practice and clinical studies.

- Determine if the quantitative change in between baseline and Month 6 is predictive for the change at Month 12.

- Determine which single component is the most predictive for the composite index of remission.

- Determine predictors for remission, according to all the different criteria at each timepoint.

- Comparison between DAS28 remission and US remission

- Prediction of remission based on US data

7. RESEARCH METHODS

7.1. Study design

This will be an observational, multicenter study, in which patients with RA will be recruited in 2 cohorts. The study design can be found in Figure 6.

The first cohort is a cohort in which the decision by the treating rheumatologist has been taken to start treatment with Enbrel as first biological product, according to prevailing reimbursement criteria in Belgium and dosing in line with the Summary of Product Characteristics (SmPC).

The second cohort is a cohort in which the decision of the treating rheumatologist has been taken to start treatment with Enbrel according to prevailing reimbursement criteria in Belgium as second biological product (either after use of another anti-TNF or another mechanism of action) and dosing in line with SmPC.

The study flow chart can be found in Table 1.

At baseline, demographics, disease duration (defined as the time between diagnosis and etanercept treatment initiation), Health Assessment Questionnaire (HAQ) and different remission criteria (DAS28, SDAI, CDAI, Boolean definition of both CDAI and SDAI, DAS28 in combination with US) will be recorded.

The evaluation will take place at Data Collection Points (DCPs) which will coincide with regular visits, not scheduled for the purpose of the study, but at Q3 months with a time window of ± one month, recording the same data, as well as current medication and related adverse events (AEs).

The ultrasound will only take place in selected centers with a proven record of US training and day-to-day clinical experience. Bruyn et al. (2013) concluded that the scoring of US intra-reader variability was excellent (κ=0.91) and inter-reader variability was good (κ=0.75).

A recently published US7 reliability study investigated the inter-observer and intra-observer reliability of sonographers, determining the US7 score under conditions similar to those of daily rheumatological practice. The median overall κ value for detecting synovitis was κ=0.51, for tenosynovitis/paratenonitis κ=0.57 and for erosions κ=0.45. This study also showed that the US7 score has the potential also in multicentre analysis to assess structural changes with moderate to good reliability (Ohrndorf et al. 2012).

Ultrasound images will be collected and saved. When needed for analysis, they can afterwards be read by central readers.

Figure 6. Study design

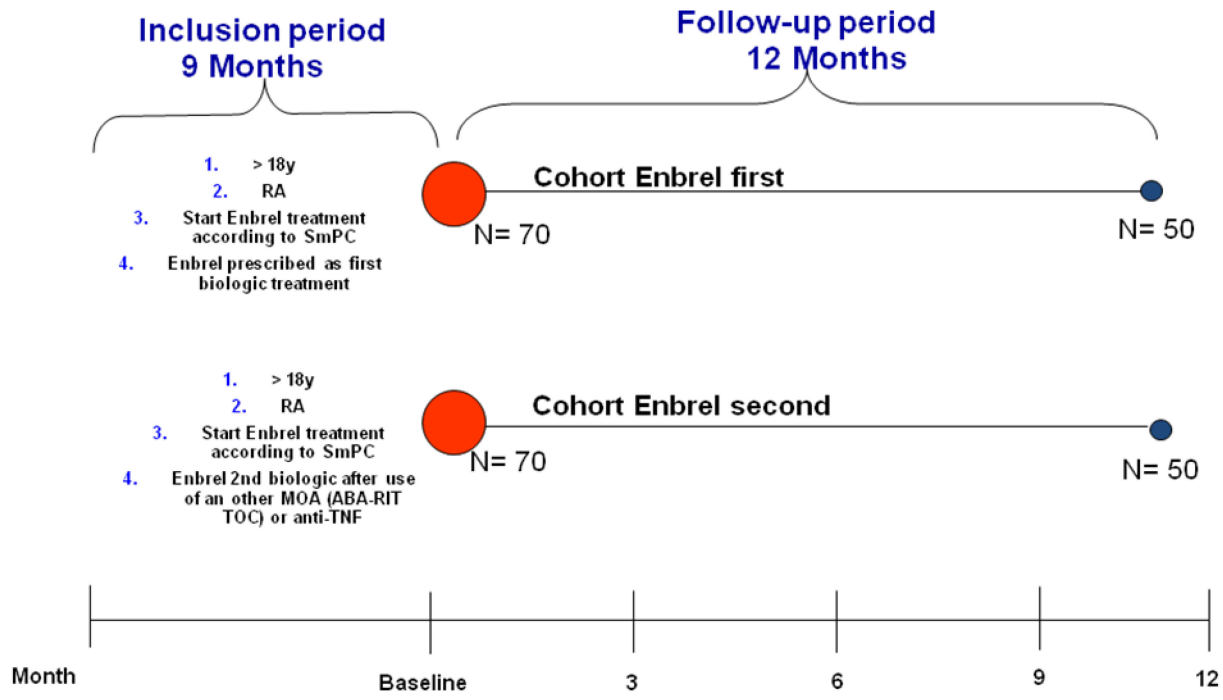


Table 1. Study flow chart

	Baseline	DCP1	DCP 2	DCP 3	DCP 4
Time	0 m	Month 3 (2-4)	Month 6 (5-7)	Month 9 (8-10)	Month 12 (11-13)
Demographics	X				
Disease duration	X				
DAS28	X	X	X	X	X
SDAI	X	X	X	X	X
CDAI	X	X	X	X	X
BOOLEAN CDAI SJC≤1, TJC≤1, PtGA≤1	X	X	X	X	X
BOOLEAN SDAI SJC≤1, TJC≤1, PtGA≤1and CRP≤1	X	X	X	X	X
Ultrasound (Selected Centers)	X		X		X
HAQ	X	X	X	X	X
Current medication	X	X	X	X	X
Adverse events	X	X	X	X	X

7.2. Setting

7.2.1. Inclusion criteria

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

1. Patients with active RA who start treatment with Enbrel according to the prevailing reimbursement criteria in Belgium and dosing in line with the SmPC.

   a) First cohort: Enbrel is the first biological product prescribed.

   b) Second cohort: Enbrel is the second biological product prescribed.

2. Capable of understanding and willing to provide signed and dated written, voluntary informed consent before any protocol-specific procedures are performed.

3. Eighteen (18) years of age or older at time of consent.

4. Evidence of a personally signed and dated informed consent document indicating that the patient (or a legally acceptable representative) has been informed of all pertinent aspects of the study.

7.2.2. Exclusion criteria

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

1. History of or current psychiatric illness that would interfere with the subject's ability to comply with protocol requirements or to give informed consent.

7.3. Variables

Table 2. Variables, roles, data sources and operational definitions

Variable	Role	Data source(s)	Operational definition
Demographics	Baseline variables	Medical records	Please refer to the SAP*
Disease duration	Baseline variables	Medical records	Please refer to the SAP*
Cohort 1 or 2	Sub-group identifier	Medical records	Please refer to the SAP*
DAS28	Outcome variable	Medical records	Please refer to the SAP*
SDAI	Outcome variable	Medical records	Please refer to the SAP*
CDAI	Outcome variable	Medical records	Please refer to the SAP*
BOOLEAN CDAI SJC≤1, TJC≤1, PtGA≤1	Outcome variable	Medical records	Please refer to the SAP*
BOOLEAN SDAI SJC≤1, TJC≤1, PtGA≤1and CRP≤1	Outcome variable	Medical records	Please refer to the SAP*

Variable	Role	Data source(s)	Operational definition
Ultrasound (Selected Centers)	Outcome variable	Medical records	Please refer to the SAP*
HAQ	Outcome variable	Medical records	Please refer to the SAP*
Current medication	Exposure	Medical records	Please refer to the SAP*
Adverse events	Safety	Medical records	Please refer to the SAP*

* SAP = Statistical Analysis Plan

7.4. Data sources

This study will be a primary data collection study. The data source will be the medical records for all variables. For all details please refer to the Statistical Analysis Plan (SAP).

7.5. Study size

It will not be possible to justify the sample size of the study on the basis of inferential statistical assumptions. Indeed, there are currently insufficient data available concerning the prediction of remission on the basis of CDAI, SDAI, DAS28, DAS28 and Ultrasound, and EULAR Boolean definition for clinical practice and clinical studies.

The analysis of the primary endpoint will be based on a logistic regression defining the dependent variable as the remission at Month 12 and the 5 independent variables as CDAI, SDAI, DAS28, DAS28 and Ultrasound, and EULAR Boolean definition for clinical practice and clinical studies.

This analysis will be conducted in each armof the study if possible as well as after pooling of both patient groups.

In this context it seems reasonable to ensure the completion of the study by a total approximate number of 100 patients (approximately 50 patients per arm). In order to ensure 50 completers in each arm, 70 patients will be recruited at baseline, taking into account a drop out rate of 30% over 1 year period. In order to have 100 evaluable patients for the predictive model and given the current recruitment status (January 26th 2015 RA 1st: 34 vs RA 2nd : 4) we will allow the needed number of patients to be recruited in whichever cohort: 1st or 2nd. This will limit the potential extension of the recruitment period.

7.6. Data management

All the data will be recorded by the Investigators and their study nurses in an electronic Case Report Form (eCRF).

The Data Management of the study will be done directly in the eCRF by the automatic generation of inconsistencies and by the manual generation of queries.

The statistical software which will be used for the analyses is the IBM-SPSS Statistics program (Version 21.0 and eventual upgrades/updates).

7.7. Data analysis

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

The analysis of the primary endpoint will be based on a logistic regression defining the dependent variable as the remission at month 12 and the 5 independent variables as CDAI, SDAI, DAS28, DAS28 and Ultrasound, and EULAR Boolean definition for clinical practice and clinical studies. This analysis will be conducted in each arm of the study as well as after a pooling of both patient groups.

The other statistical methods used for the analysis of the data will be mainly descriptive.

Appropriate inferential analyses will be used to compare the over-time modifications of study parameters and potentially to compare the two arms of the study.

Time to event variables will be analyzed using the Kaplan-Meier's method with comparison between groups being ensured by the log rank test.

An interim analysis of baseline data will be performed at Month 6.

7.8. Quality control

The sponsor will perform quality control and assurance checks of the study. Before enrolling any subjects in this study, sponsor personnel and the investigator will review the protocol, the SmPC, the eCRF and the instructions for their completion, the procedure for obtaining informed consent, and the procedure for reporting AEs and serious adverse events (SAEs).

A qualified representative of the sponsor will monitor the conduct of the study by visiting the site and by contacting the site by telephone. During the visits, information recorded on the eCRFs will be verified against source documents. Automatic inconsistencies will be generated by the ePlatform directly in the eCRF and Clinical Research Associates will have the opportunity to add manual queries directly in the eCRF.

All statistical programs used to manage and analyze the data will be validated and archived with the clinical database.

7.9. Limitations of the research methods

The limitations of the study are intrinsic to its observational, non-controlled, non-randomized design.

7.10. Other aspects

Not applicable.

8. PROTECTION OF HUMAN SUBJECTS

8.1. Patient Information and Consent

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

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

The informed consent form used in this study, and any changes made during the course of the study, must be prospectively approved by both the Institutional Review Board (IRB), the Independent Ethics Committee (IEC) and Pfizer before use.

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

8.2. Patient withdrawal

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

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

8.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

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

8.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in *Guidelines for Good Pharmacoepidemiology Practices* issued by the International Society for Pharmacoepidemiology, Good Epidemiological Practice guidelines issued by the International Epidemiological Association, Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research, International Ethical Guidelines for Epidemiological Research issued by the Council for International Organizations of Medical Sciences, European Medicines Agency, European Network of Centres for Pharmacoepidemiology and Pharmacovigilance, Guide on Methodological Standards in Pharmacoepidemiology.

9. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

9.1. Requirements

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

Table 3. **Requirements for recording and reporting safety events**

Safety event	Recorded on the eCRF	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All	All
Non-serious AE	All	None: Even if the study involves a site of the European Economic Area (EEA), the study team decided that the non-serious adverse events should not be reported to Pfizer Safety because none of the objectives of the study involves the active collection of safety information and the clinical team doesn't want to actively seek any specific non-serious adverse events.
Scenarios involving exposure to a drug under study, including EDP, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE)

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

Safety events listed in the table above must be reported to Pfizer within 24 hours of awareness of the event by the investigator **regardless of whether the event is determined by the investigator to be related to a drug under study**. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up)

information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.
For safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the eCRF. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Any information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

9.1.1. Reporting period

For each patient, the safety event reporting period begins at the time of the patient's first dose of Enbrel®, and lasts through the end of the observation period of the study, which must include at least 28 calendar days following the last administration of a drug under study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. If a patient was administered a drug under study on the last day of the observation period, then the reporting period should be extended for 28 calendar days following the end of observation.
If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the SAE to be related to Enbrel®, the SAE also must be reported to Pfizer Safety.

9.1.2. Causality assessment

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

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

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

9.2. Definitions of safety events

9.2.1. Adverse events

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

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

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

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

Abnormal test findings

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

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

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

9.2.2. Serious adverse events

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

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

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

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

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or

laboratory findings indicating an infection in a patient exposed to a Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

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

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

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

9.2.3. Scenarios necessitating reporting to Pfizer Safety within 24 hours

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

Exposure during pregnancy

An EDP occurs if:

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

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

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

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

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

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

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

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

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

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

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs

when the investigator assesses the infant death as related or possibly related to exposure to investigational product

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

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

Exposure during breastfeeding

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

Medication error

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

Medication errors include:

- Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);

- Confusion with regard to invented name (e.g., trade name, brand name).

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

- Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.

- Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:

    - An identifiable reporter;

- A suspect product;
- The event medication error.

Overdose, Misuse, Extravasation

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

Lack of Efficacy

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

Occupational Exposure

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

9.3. Single reference safety document

The Enbrel® SmPC will serve as the single reference safety document during the course of the study, which will be used by Pfizer safety to assess any safety events reported to Pfizer Safety by the investigator during the course of this study.

The single reference safety document should be used by the investigator for prescribing purposes and guidance.

10. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

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

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

11. REFERENCES

Backhaus M, Ohrndorf S, Kellner H, et al. Evaluation of a novel 7 joint ultrasound score in daily rheumatologic practice: a pilot project. *Arthritis Rheum* 2009; 61: 1194-201

Brown AK, Using ultrasonography to facilitate best practice in diagnosis and management of RA. *Nat. Rev. Rheumatol.* 2009: 5: 698–706.

Bruyn GAW, Hanova P, Iagnocco A, D'Agostine M-A, et al. on behalf of the OMERACT Ultrasound Task Force. Ultrasound definition of tendon damage in patients with rheumatoid arthritis. Results of a OMERACT consensus-based ultrasound score focussing on the diagnostic reliability. *Ann Rheum Dis* doi:10.1136/annrheumdis-2013-203596.

Dougados M, Jousse-Joulin S, Mistretta F, et al. Evaluation of several ultrasonography scoring systems for synovitis and comparison to clinical examination: results from a prospective multicentre study of rheumatoid arthritis. *Ann Rheum Dis*. 2010: 69:828-33.

Iagnocco A, Perella C, Naredo E, Meenagh G, Ceccarelli F, Tripodo E, Basili S, Valesini G. Etanercept in the treatment of rheumatoid arthritis: clinical follow-up over one year by ultrasonography. *Clin Rheumatol*. 2008: 27:491-6.

Ohrndorf S, Fischer IU, Kellner H, et al. Reliability of the novel 7 joint ultrasound score (US7): results from an inter-and intra-observer study performed by rheumatologists. *Arthritis Care Res* (Hoboken) 2012; 64:1238-43.

Prince FHM, Bykerk VP, Shadick NA, Lu B, Cui J, Frits M, Iannaccone CK, Weinblatt ME, Solomon DH. Sustained rheumatoid arthritis remission is uncommon in clinical practice. *Arthritis Research & Therapy*. 2012: 14: R68.

Scheel AK, Hermann KG, Kahler E et al. A novel ultrasonographic synovitis scoring system suitable for analyzing finger joint inflammation in rheumatoid arthritis. *Arthritis Rheum* 2005; 52: 733-43

Szuklarek M, Court-Payen M, Jacobsen S et al. Interobserver agreement in ultrasonography of the finger and toe joints in rheumatoid arthritis. *Arthritis Rheum* 2003; 48: 955-62

Wakefield RJ, D'Agostino MA, Naredo E, Buch MH, Iagnocco A, Terslev L, Ostergaard M, Backhaus M, Grassi W, Dougados M, Burmester GR, Saleem B, de Miguel E, Estrach C, Ikeda K, Gutierrez M, Thompson R, Balint P, Emery P. After treat-to-target: can a targeted ultrasound initiative improve RA outcomes? *Postgrad Med J.* 2012: 88: 482-6.

12. LIST OF TABLES

13. LIST OF FIGURES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.