Title	- ADEQUATE STUDY - A prospective, multicenter non-interventional study to evaluate the efficacy of Enbrel® (etanercept) over a period of 12 months in the routine treatment of patients with rheumatoid arthritis, axial spondyloarthritis, psoriatic arthritis, or plaque psoriasis with particular focus on the clinical status improvements still observable after 12 weeks of treatment.
Study number:	B1801385
Version:	Final 1.3
Date:	30.01.2015
Name of active substance:	Enbrel® (etanercept)
Scientific question and goals	The goal of this non-interventional study is to evaluate the efficacy of etanercept during routine clinical use over a maximum of 12 months in patients with rheumatoid arthritis, psoriatic arthritis, axial spondyloarthritis, or plaque psoriasis. In so doing, particular attention will be paid to the proportion of those patients who only attain the desired treatment goal after 12 weeks of treatment. The primary efficacy end point for the study is the proportion of patients who attain the desired treatment goal after 12 and 24 weeks, whereby data collection tools including DAS28, PASI, PGA, and ASDAS will be used to define the indication-specific treatment goal in accordance with the currently valid national/international treatment guidelines and -recommendations. The secondary efficacy end points for the study include not only objective measures of disease activity but also patient-reported

	information regarding function. Safety and tolerability of the treatment are recorded based on the documentation of adverse events and the reasons for premature ending of treatment.
Author	Dr. PPD Pfizer Pharma GmbH Linkstr. 10 10785 Berlin

[redacted]

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1. **LIST OF ABBREVIATIONS**

Abbreviation	**Definition**
AMG	Arzneimittelgesetz [German Drug Act]
ASDAS	Ankylosing Spondylitis Disease Activity Score
AXSPA	Axial spondyloarthritis
BASDAI	Bath Ankylosing Spondylitis Disease Activity Index
BSA	Body Surface Area
ESR	Erythrocyte sedimentation rate
CDAI	Clinical Disease Activity Index
CRF	Case Report Form
CRP	C-reactive protein
CSR	Clinical Study Report
DAS	Disease Activity Score
DLQI	Dermatology Life Quality Index
DSU	Drug Safety Unit
DVP	Data Validation Plan
EIU	Exposure in Utero
ETN	Etanercept
EULAR	European League Against Rheumatism
FDAAA	Food and Drug Administration Amendments Act
FFbH	Hannover Functional Questionnaire
GCP	Good Clinical Practice
GPP	Good Pharmacoepidemiology Practice
IEC	Independent Ethics Committee
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
LDAS	Low Disease Activity Score
LSLV	Last Subject Last Visit
MDA	Minimal Disease Activity
MTX	Methotrexate
PASI	Psoriasis Area and Severity Index
PCD	Primary Completion Date
PhRMA	Pharmaceutical Research and Manufacturers of America
PRO	Patient-Reported Outcome(s)

PsA	Psoriatic Arthritis
PSARC	Psoriatic Arthritis Response Criteria
PsO	Plaque Psoriasis
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
SAP	Statistical Analysis Plan
SDAI	Simple Disease Activity Index
SAE	Serious Adverse Event
AE	Adverse Event
VAS	Visual Analog Scale

2. RESPONSIBILITIES

Scientific Director

Name	Title	Office	Address
Dr. PPD	Study PPD	Pfizer Pharma GmbH	Linkstrasse 10; 10785 Berlin
Dr. PPD	Scientific PPD	Center for Innovative Diagnostics and Treatment - Rheumatology/ Immunology at the Goethe University Hospital, Frankfurt	PPD Frankfurt am Main
PD Dr. PPD	Scientific PPD	Charite – Berlin University Medical Center	PPD Berlin
Dr. PPD	Scientific PPD	Ruhrgebiet Rheumatology Center	PPD Herne
Prof. Dr. PPD	Scientific PPD	Schleswig-Holstein University Hospital, Lübeck Campus	PPD Lübeck

3. ABSTRACT

An abstract is not required.

4. AMENDMENTS AND UPDATES

Currently not applicable.

5. MILESTONES

Milestone	Planned date
Start of data collection	01. February 2015
End of data collection	31. July 2017
Final study report	30. June 2018

6. RATIONALE AND BACKGROUND INFORMATION

6.1. Background information

For patients with rheumatic diseases, attaining remission or at least low disease activity and close monitoring result in more favorable statuses which are visible in radiology findings and functionally measurable [1-3]. If remission cannot be attained, at least a low level of disease activity should be achieved, as is often the case especially with a long-persisting disease. The German treatment guidelines for rheumatoid arthritis indicate that the desired treatment goal should be attained after 3 months and in any case after no more than 6 months [4]. The same approach also applies accordingly for other indications.

For psoriatic arthritis (PsA), criteria according to PSARC and the extent of body surface area (BSA) affected are also used to assess disease activity in patients with PsA [5]. For axial spondyloarthritis (axSpA), the most proven parameters for the assessment of disease activity are ASDAS or BASDAI [6]. The assessment of disease activity in plaque psoriasis (PsO) is usually performed using PASI, BSA, and DLQI [7, 8].

The COMET study has shown that RA patients who start treatment with etanercept early on are more likely to attain clinical remission. In this study, the DAS remission criteria were attained after 24 weeks by 50 % of the patients, which constituted a further 40 % increase versus the status attained at week 12. After 52 weeks, 57 % of the patients had attained the remission criteria [9].

In the PRISTINE study, Strohal was able to show that 37.2 % of the patients with PsO who were treated once weekly had attained a PASI75 after 12 weeks (62.4 % when treated with 50 mg twice weekly). The number of patients who attained a PASI75 increased to 59.9 % after 24 weeks (78.2 % when treated with 50 mg twice weekly) [10].

These studies show clearly that it may be worth continuing treatment with etanercept beyond 12 weeks even if the criterion for low disease activity has not yet been attained.

6.2. Study rationale

Approx. 20 - 30 % of patients end their treatment with etanercept during the first year of treatment, whereby the discontinuation of treatment is due to a lack of efficacy or side effects. The German and also the EULAR guidelines for the treatment of RA recommend a change of treatment after 3 and at most after 6 months if the criterion for low disease activity has not been attained [4, 11, 12]. The treatment guidelines for the other indications for which etanercept is approved are similar.

Clinical studies in the indications of RA, axSpA, PsA, and PsO show that it may be worth continuing treatment beyond a period of 12 weeks even if the criterion for low disease activity has not yet been attained, because the number of patients who only attain this criterion beyond the 12 weeks is increasing.

In routine care, according to national and EULAR guidelines, the medical assessment of the treating rheumatologist or dermatologist and other criteria should be taken into consideration in addition to the purely numerical assessment of treatment goals. Therefore, the assessment as to whether the treatment goals were ultimately attained depends in everyday clinical practice not only on the numerical results from the DAS, ASDAS (or PSARC) or PASI tools, but also on the overall evaluation of the physician and the patient, as well as on the treatment outcomes reported by the patient ("patient reported outcomes," PRO), treatment satisfaction, and other social and functional factors.

In summary, it is therefore the primary goal of this study to check how many patients in everyday clinical practice benefit from the continuation of treatment with etanercept beyond 12 weeks, even if the defined treatment goal has not yet formally been attained at that time but treatment is continued based on the judgment of the prescribing physician and the patient. In so doing, this rate is to be compared across the different indications. The variables which also reflect compliance with the treatment guidelines by physicians are to be examined in terms of additional influencing factors such as disease duration, concomitant medications, or PROs.

Early treatment with biologics is recommended for all indications in order to attain improved quality of life and patient function and to exert a favorable effect on comorbidities, e.g. cardiovascular diseases. It is not yet known whether the burden of disease is comparable in the different indications at the start of treatment with etanercept. Here, a better understanding of these relationships could help doctors to determine the optimal time point for the start of treatment with etanercept.

In this study, the variables are examined in a joint study setting (as far as is currently known, for the first time), which permits these variables to be compared directly across the different indications. Even though the treatment goals and the extent of disease activity in the different indications are determined based on different tools, it will still be possible to measure and compare PROs in particular, such as global assessment, pain, fatigue, mental health and - at least for the rheumatological indications - FFbH (comparable with the HAQ) and morning stiffness, regardless of the indication. The overall physician's assessment will also be measured in all indications and compared between the individual indications.

In addition to findings regarding relevance to practice and the reality of care according to treatment guidelines and recommendations, patient compliance with the treatment plan will be scientifically studied in detail.

The goal of Pfizer's own "TOGETHER" program is to improve patient treatment compliance with training measures. This study is to investigate the extent to which participation in the "TOGETHER" program influences treatment compliance.

7. SCIENTIFIC QUESTION AND GOALS

The primary goal of this study is to determine how many patients treated under everyday conditions benefit from the continuation of treatment with etanercept beyond 12 weeks even if the desired treatment goal (see Table 2) has not yet been attained at that time point, as well as to compare these rates across the different indications. For this purpose, the following questions are to be answered based on a reliable data body collected during clinical routine:

- Proportion of patients who have not attained defined treatment goals for each respective indication after 12 weeks, but do attain these between weeks 12 and 24.
- Proportion of patients who have attained the desired treatment goal after 12 weeks,
- Proportion of patients who continue treatment up to week 52 in the different indications,
- Comparison of PRO results across indications,
- How is the decision made in everyday clinical practice whether treatment with etanercept is continued or discontinued (i.e. which other parameters are taken into consideration, for example PRO or physician's global assessment),
- At what time point is the decision made to switch treatment (i.e. after 3 or 6 months, or even later),
- Are there predictive factors for the continuation of treatment with etanercept,
- What factors may influence treatment compliance (e.g. participation of the patients in a compliance program).

8. STUDY METHODS

8.1. Study design

8.1.1. Design and study procedures

This study is a prospective, multicenter, non-interventional study to evaluate the efficacy of etanercept in patients with RA, PsA, axSpA or PsO.

Efficacy data will be documented within a period of 12 months and health outcomes every quarter in the course of routine treatment. An overview of the documentation to be performed can be found in Table 1 below.

Table 1: Overview of study procedures

	Visit 1 Week 0	Visit 2 Week 12	Visit 3 Week 24	Visit 4 Week 36	Visit 5 Week 52
Medical history	X				
Inflammation in MRI (axSpA)	X				
Radiological Sacroiliitis (axSpA)	X				
Participation in the "Together" program	X				
Inclusion/exclusion criteria	X				
Treatment/medications					
Prior treatment	X				
Treatment with Enbrel	X	X	X	X	X
Concomitant treatment		X	X	X	X
Safety parameters					
Physical examination	X				
Laboratory	X	X	X	X	X
AE documentation		X	X	X	X
Efficacy					
Examination of joints	X	X	X	X	X
PASI (PsO)	X	X	X	X	X
Morning stiffness (RA, axSpA, PsA)	X	X	X	X	X
Patient and physician global assessment	X	X	X	X	X
Pain	X	X	X	X	X
Fatigue	X	X	X	X	X
Occiput-to-wall distance (axSpA)	X	X	X	X	X
Dactylitis (PsA)	X	X	X	X	X
Nail involvement (PsO, PsA)	X	X	X	X	X
Enthesitis (PsA, axSpA)	X	X	X	X	X
Pruritus (PsO)	X	X	X	X	X
Health outcomes					
FFbH (RA, axSpA, PsA)	X	X	X	X	X
BASDAI (axSpA)	X	X	X	X	X

DLQI (PsO)	X	X	X	X	X
PHQ-2	X	X	X	X	X

8.1.2. Primary study end points

- Patients with RA: Proportion of patients who attain the desired treatment goals (see Table 2) at the week 12 and week 24 time points under monotherapy or in combination with MTX and maintain these long-term over a period of 52 weeks.
- Other indications: Proportion of patients who attain the desired treatment goals according to guidelines (see Table 2) in each respective indication at the week 12 and week 24 time points.

8.1.3. Secondary end points at weeks 12, 24, 36, and 52

All patients:

- Proportion of patients who continue treatment with etanercept,
- Occurrence of adverse events,
- Remission,
- Patient global assessment,
- Fatigue,
- Pain (VAS),
- Physician global assessment,
- PHQ-2
- Comparison of the parameters "patient global assessment," "fatigue," "pain," "physician global assessment," and " PHQ-2 across all indications,
- Comparison of FFbH and morning stiffness among patients with RA, axSpA, and PsA,
- Discontinuation of treatment due to a lack of efficacy or adverse events,
- Nature of further treatment if treatment has been discontinued,

Additionally for RA patients:

- FFbH
- CDAI
- SDAI

Additionally for axSpA patients:

- BASDAI,
- FFbH
- Enthesitis
- Occiput-to-wall distance

Additionally for PsA patients:

- BSA

- Dactylitis
- Enthesitis
- FFbH

Additionally for PsO patients:

- PASI, median time to PASI75, body segment (head, trunk, upper and lower extremities) and component-related subscales (erythema, induration, flaking) over 24 weeks,
- DLQI,
- Pruritus
- BSA.

The following indication-related laboratory tests will be documented if they are available as part of a routine assessment:

- Erythrocyte sedimentation rate (ESR), C-reactive protein (CRP)

In addition, the following laboratory tests will be documented for patients with RA, PsA, and axSpA if they are available as part of a routine assessment:

- Rheumatoid factor (RF) and anti-CCP antibodies.
- HLA-B27 at Visit 1 (just axSpA).

8.2. Study setting

8.2.1. Study conduct

The planned recruitment period is 18 months. With a planned observation duration of 12 months per patient, the entire study would thus last for 30 months. The study is to start in Q1/2015 and will be ended in Q3/2017. In all, about 2100 patients in 300 centers are to be included in this non-interventional study, of whom about 1200 will have a diagnosis of RA and about 300 each will have a diagnosis of axSpA, PsA, and PsO.

After regular initiation on treatment with etanercept, patients will be documented for a period of up to 12 months. In accordance with section 67, paragraph 6 of the AMG, notice of the conduct of the study will be made to the National Association of Statutory Health Insurance Physicians, the Central Federal Association of Health Insurance Funds, and the competent central federal authority. Logistics, database creation, data input, and evaluation and reporting will be performed by a CRO Winicker Norimed.

Due to the high number of participating centers and patients throughout Germany, it is expected that the results from the study will have a representative nature. Another advantage of the study design lies in the fact that the 4 different indications will be examined within one study setting, which should improve the comparability of the study results across indications.

8.2.2. Inclusion criteria

Patient eligibility should be checked and documented by the treating physician before patients are included in the study. The decision to commence treatment with etanercept shall be made in advance and independently of any participation in this study.

Proof of a personally signed and dated informed consent form stating that the patient (or legal representative, if applicable) has been informed of all concrete aspects of the study is a prerequisite for inclusion in this study.

Patients eligible for documentation must meet the following criteria,:

1. Confirmed diagnosis of RA, axSpA, PsA or PsO,

2. No prior treatment with etanercept and eligibility for treatment with etanercept according to the summary of product characteristics,

3. Patient age $\geq$18 years,

8.2.3. Exclusion criteria

The contraindications, special warnings, and precautions according to the summary of product characteristics for etanercept shall apply. The additional documentation of the patient in another post-marketing study with etanercept is not permitted.

8.3. Variable description

The primary and secondary end points are listed in section 8.1.2 and section 8.1.3.

All of the indication-specific efficacy measures used in this study, such as DAS28, BASDAI or PASI, are clearly defined and meet the current international scientific standard. The definitions for “desired treatment goals” in the individual indications were based on recommendations, including from national and international treatment guidelines. An overview of these recommendations can be found in Table 2 below.

Table 2: Overview of desired treatment goals and minimum efficacy criteria in the different approved etanercept indications, based on the current latest treatment guidelines

Indication	Desired treatment goal	Minimum efficacy	Source
PsO	• PASI75 or • PGA ("clear" or "almost clear") and • DLQI 0 or 1	• PASI50 and • DLQI <5 or improvement of at least 5 points	S3 Guidelines for the systemic treatment of PsO [7, 8]
RA	• DAS28 <2.6	• DAS28 ≤3.2 or • Physician assessment, e.g. based on radiology findings	S1 Guidelines of the DGRh [4]
axSpA	• ASDAS <1.3	• BASDAI: 50% relative difference or absolute difference of 2 points (scale from 0 -10) and • Expert opinion on continuation: yes/no	Kiltz et al. 2014 [13]
PsA	• DAS28 <2.6 or • MDA criteria met [a]	• DAS28 ≤3.2 or • Physician assessment, e.g. based on radiology findings	a) Mease 2011 [5]

Selected parameters, such as remission, low disease activity, or continuation of treatment, will be analyzed for potential influencing variables (e.g. duration of disease, clinical outcomes, PRO).

Detailed information on the calculation of variables and on data evaluation in general will be set forth in a separate statistical analysis plan (SAP) before the start of the evaluation.

8.4. Source documents

The data will be recorded using a case report form (CRF) for each patient included. The CRF contains the queries and questionnaires required for all four indications; the indication-specific queries and questionnaires are to be completed for each indication and must be handed out to the patients. The completed original CRFs are the sole property of Pfizer and must not be provided to third parties in any format without the written approval of Pfizer, with the exception of authorized representatives of Pfizer or the appropriate competent authorities.

The treating physician is ultimately responsible for the collection and reporting of all clinical data, safety and laboratory data entered on the CRFs and other forms for data collection (source documents) and must guarantee that they are accurate, authentic/original, traceable, complete, consistent, legible, timely (contemporaneous), permanent, and available as required. The CRFs must be signed by the treating physician or authorized personnel. All corrections of entries on the CRFs and source documents must be dated, signed off, and explained (if required) and must not obscure the original entry.

In most cases, the source documents are patient records in the hospital or at the doctor's office. In these cases, the data collected on the CRFs must match the data in these records.

In some cases, the CRF or part of the CRF can also serve as a source document. In these cases, a document must be available at the doctor's study site and at Pfizer and must clearly identify the data recorded in the CRF and for which the CRF is considered a source document.

The clinical parameters recorded, especially those used to assess efficacy, are usual, known and recognized variables within each respective indication. All questionnaires used in the study have been validated.

8.5. Calculation of case numbers

It is assumed that the RA patients included in this study who are receiving a combined treatment (ETN + MTX) will be similar to those patients included in the randomized, double-blind DOSERA study in terms of the proportion of patients continuing treatment beyond week 12 (i.e. adequate efficacy - defined based on the DAS28 and the patient and physician global assessment of disease progression - has been attained). In that study, 22 - 26 % of the patients on combined treatment had attained no adequate efficacy after 12 weeks and continued treatment with etanercept (open-label), while conversely, adequate efficacy from treatment had been attained for 74 - 78 % of the patients at week 12. The sample size for this non-interventional study was calculated with the primary focus on the indication of RA.

Assuming that 74% of the patients under treatment with ETN + MTX and 66% of the patients under ETN monotherapy exhibit adequate response to treatment after 12 weeks (odds ratio of 0.682), 1200 patients (with a 2:1 ratio, this equals 800 patients under combined treatment and 400 patients under monotherapy) will be sufficient to detect a significant difference in the primary end point "proportion of patients attaining the desired treatment goal" with a power of 80% using a two-sided test with a significance level of 5%.

A logistic regression quoting the odds ratio and the corresponding 95% confidence interval is the appropriate statistical methodology for the analysis of this binary variable. As a sensitivity analysis, a GEE (generalized estimating equation) analysis can also be performed as a repeat method to obtain the binary response variable.

Because the combination with MTX is not recommended for the indications axSpA, PsO, and PsA, the inclusion of 300 patients in each of these indications appears sufficient for analysis of efficacy and tolerability.

8.6. Data management

The completed CRFs will be sent by mail from the center to the CRO. Data will be entered at the CRO into an SAS-based database. All entries will be recorded in an audit trail file.

8.7. Data analysis

Absolute and relative adjusted frequencies are determined for categorical data. Numerical data are expressed using the sample statistics mean and standard deviation, as well as minimum, 1% percentile, 5% percentile, lower quartile, median, upper quartile, 95% percentile, 99% percentile and maximum.

The primary end point "proportion of patients attaining the desired treatment goal" will be analyzed using a logistic regression for the subgroups "RA patients with ETN+MTX" and "RA patients with ETN monotherapy".

A detailed description of the statistical analysis of the data collected will be included in the SAP which will be dated, stored, and maintained by the sponsor. The SAP may modify the analyses described here. Every substantial amendment to the definition and analysis of the primary end point would take place in the form of a protocol amendment.

8.8. Quality control

Plausibility checks for the data entered will be defined in a data validation plan (DVP). As far as possible, these checks will be performed with software support and in the event of deviations, queries will be sent by the CRO to the centers. The sending and return of queries

will be tracked and if necessary, data changes will be performed in the database. All of the changes performed will be recorded in an audit trail file.

Furthermore, there it is provisionally planned that 30 monitoring visits will be performed at randomly selected centers to ensure data quality and to verify the documented patient data.

8.9. Strengths and limitations of the study methodology used

An inherent disadvantage of a non-controlled observational study is the potential risk of selection bias. Furthermore, patients who have withdrawn prematurely from the study, whose missing observations are not usually replaced, may skew the time point results toward the end of the study. Also, no proof of efficacy is possible in the classical sense as the data from a randomized parallel group are not available as a control.

However, these limitations are balanced by advantages associated with the methodology. For example, the design of an observational study usually permits the inclusion of a substantially larger number of patients that would be usual in randomized, controlled studies. Furthermore, in randomized clinical studies, only strictly selected patient groups are studied, which limits the applicability of these studies in terms of the patients who are ultimately treated in routine clinical practice. In the case of RA, it was shown based on evaluation of the German biologicals registry RABBIT that only 21 - 33% of the registry patients treated in routine clinical practice with TNF blockers would also have been eligible for participation in the pivotal randomized, controlled studies [14]. The patient groups selected from the clinical RA studies this reflect are only a small proportion of the patients who are routinely treated with biologicals in the postmarketing phase. As such, non-interventional observational studies, despite the limitations mentioned above, are capable of providing valuable supplemental information on the effects of a medication in everyday clinical practice.

8.10. Other aspects

Not applicable.

9. **PROTECTION OF STUDY PARTICIPANTS**

9.1. Patient information and informed consent form

All parties guarantee the protection of the patient's personal data and will not include the name of the patient in any forms from Pfizer, reports, publications or other disclosures unless required by law. In the event that data is forwarded, Pfizer will maintain high standards of confidentiality and the protection of the patients' personal data.

The informed consent form used in this study and all changes made in the course of the study must be approved in advance by Pfizer and submitted to the IRB/IEC for review before use.

The treating physician must guarantee that every study patient or her/his legal representative is informed fully of the characteristics and goals of the study and the potential risks associated with participation. The treating physician or a person assigned by her/him shall obtain a written informed consent form from every patient or patient's legal representative before study-specific activity is performed. The treating physician shall keep the original of every informed consent form signed by the patient.

9.2. Ending the participation of a patient

The patient can withdraw her/his consent to participate in the non-interventional study at any time or the treating physician may decide to end the participation of the patient on grounds of safety, problems with compliance, or for administrative reasons. In any case, the patient's clinical status should be documented if possible. The physician should ask the patient about the reasons for her/his decision and continue to track all unresolved adverse events.

If the patient withdraws her/his consent for further data collection, data will no longer be recorded from her/him as part of the non-interventional study.

9.3 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The observational protocol and the patient information and informed consent form will be submitted to the competent ethics committee for review before patients are included.

9.4 Ethical study conduct

This study is a multicenter, prospective, non-interventional study in accordance with section 4, number (23), clause 3 of the AMG. Furthermore, the vfa recommendations for the improvement of quality and transparency in non-interventional studies apply, as do the guidelines of the *"Good Pharmacoepidemiology Practices"* (GPP), issued by the "International Society for Pharmacoepidemiology" (ISPE), the guidelines of the "International Society for Pharmacoeconomics and Outcomes Research" (ISPOR), and the guidelines of the "Pharmaceutical Research and Manufacturers of America" (PhRMA).

The patient shall provide her/his written informed consent form for the study, which will have been submitted to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) for review beforehand.

Based on the the vfa recommendations for the improvement of quality and transparency in non-interventional studies and in order to satisfy the requirement for publication of notice of NISs, this non-interventional study will be registered in a publicly accessible registry.

10. MANAGEMENT AND REPORTS FROM ADVERSE EVENTS/ADVERSE DRUG REACTIONS

10.1. Summary of product characteristics

Etanercept shall be used in accordance with the summary of product characteristics. The specified contraindications, warnings and precautions for use, undesirable effects, interactions, and information on posology and method of administration must be followed. All drug safety-relevant cases reported by the participating physician to the CRO contracted by Pfizer, Winicker Norimed, in the course of this non-interventional study will be evaluated based on the summary of product characteristics.

10.2. Requirements

The table below summarizes the requirements for the recording of safety-relevant events on the reporting form for adverse event monitoring (AEM) in non-interventional studies to Winicker Norimed. These requirements are described for three types of events: (1) serious adverse events (SAEs); (2) non-serious adverse events (if applicable) and (3) scenarios under which drug exposure occurs, including exposure during pregnancy, exposure during lactation, medication errors, overdose, misuse, extravasation, and job-related exposure. These events are defined in the section "Definitions of safety-relevant events".

safety-relevant event	Notation in the case report form	Reporting on the NIS-AE reporting form to Winicker Norimed within 24 hours after discovery
SAE	All	All
Non-serious AE	all	all
Scenarios under which drug exposure occurs, including exposure during pregnancy, exposure during lactation, medication errors, overdose, misuse, extravasation, and job-related exposure.	All	All (regardless of whether they are associated with an AE)

For each adverse event (AE) the physician must track and collect information suitable for determining the outcome of the adverse event and for assessing whether it meets the classification criteria for an SAE (see the section "Serious adverse events" which follows).
Safety-relevant events from the above table must be reported by the physician to Winicker Normied within 24 hours after s/he becomes aware of the event, **regardless of whether s/he sees any causal relationship with the medication being studied.** Especially when the serious

adverse event is fatal or life-threatening, the report to Winicker Normied must be made immediately, regardless of the scope of information available about the event.

These deadlines also apply for additional new information (follow-up) regarding reports of safety relevant events already submitted.

In the rare case that the physician is not immediately aware of the occurrence of a safety-relevant event, the physician must report the event within 24 hours after s/he becomes aware of it and must document the time at which s/he discovered the adverse event.

For safety-relevant events categorized as serious or listed in the right-hand column of the above table, which must be reported to Winicker Normied within 24 hours after they are discovered, the physician is obligated to track information and report it to Winicker Normied within the 24-hour deadline. Furthermore, a physician may be asked by Winicker Normied to expedite the collection of certain additional information. Such information may go beyond the scope and detail of the information about adverse events recorded in the case report form. Generally, this will involve the description of the adverse event in sufficient detail to permit a comprehensive medical evaluation of the case and independent determination of the possible causality. Also, all additional relevant information about the event, e.g. concomitant medications and illnesses, must be provided.

If a patient dies, a summary of any available autopsy findings must be submitted to Winicker Normied as soon as possible.

10.3. Reporting period

For each patient, the reporting period for reporting adverse events starts with the time of first use or with the time of informed consent if he/she is already using etanercept. The reporting period will last until the end of the observation period for the study and at least 28 calendar days after the last administered dose of the medication being observed. All safety-relevant events from the above table occurring within this reporting period must be reported to Winicker Norimed and its authorized representative.
In most cases, the date of informed consent is the same as the date of inclusion of the patient in the NIS. In some situations, there might be a time gap between the date of informed consent and the inclusion date. If in such cases a patient provides informed consent but is never included in the study (e.g. the patient changes her/his mind regarding participation, then the reporting period will end with the date of the decision not to include the patient.
Serious adverse events occurring after the end of the non-interventional study (NIS) and the observation period must also be reported to DSU if the physician sees a causal relationship with etanercept.

10.4. Causality assessment

The physician must assess and document the causal relationship. For all AEs, the physician must collect sufficient information to determine the causality of each adverse event. For an AE with a causal relationship with etanercept, the physician must track this until the event

and/or its sequelae have resolved or have stabilized at an acceptable level for the physician and Pfizer agrees with this assessment.

The physician's causality assessment shall include determination whether there is a possibility that etanercept has caused the adverse event or contributed thereto. Even if the final causality assessment by the physician is "unknown" and the physician cannot determine whether the event was caused by etanercept, the safety-relevant event must be reported within 24 hours.

If the physician is unable to identify the cause of the event but decides that etanercept has not caused the event, this fact must be documented clearly on the NIS AE reporting form.

10.5. Definition of safety-relevant events

10.5.1. Adverse events

An adverse event (AE) is any adverse medical incident occurring with a patient who is using a medicinal product. The event does not necessarily have to be causally related to the treatment or use. The same definition applies for medical devices and nutritional supplements (including baby and children's foods [hereinafter - pediatric preparations].

Examples of adverse events include in particular but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding counts as an adverse event)
- Clinically relevant signs and symptoms
- Changes in findings from physical examination
- Hypersensitivity and allergic reactions
- Lack of efficacy
- Drug abuse
- Drug dependency

In addition, symptoms or findings may be included which are attributable to the following:

- Overdose of a substance
- Drug withdrawal
- Misuse
- Use outside the approved indication (off-label use)

- Drug interactions
- Extravasation
- Exposure in utero
- Exposure during lactation
- Medication error
- Job-related exposure

Abnormal test findings

An abnormal objective test finding must be reported as an adverse event if:

- the test finding is accompanied by symptoms and/or
- the test finding requires further diagnostic tests or medical/surgical intervention and/or
- the test finding results in a change to the dose of the medicinal product being observed or in the ending of the study for the study participant concerned, in substantial additional concomitant drug treatment, or in other treatment and/or
- the test finding is categorized as an adverse event by the physician or sponsor.

The mere repetition of an abnormal test for which none of the above conditions apply is not considered an adverse event. Abnormal test findings which are interpreted as erroneous do not need to be reported as adverse events.

10.5.2. Serious adverse events

A serious adverse event is any adverse medical incident after the administration of a medicinal product or nutritional supplement (including pediatric preparations) or after the use of a medical device which, regardless of the dose:

- Results in death
- Is life-threatening
- Requires hospitalization of the patient or prolongation of hospitalization (see below for circumstances which do not count as an adverse event)
- Results in permanent or substantial disability/loss of work capacity (substantial impairment of the ability to perform everyday activities)

- Results in a congenital deformity/birth defect.

Furthermore, medically significant adverse events must be categorized as "serious". It must be reviewed in accordance with medical and scientific discretion whether an event must be evaluated as **medically significant**. Events are medically significant if they are not necessarily immediately fatal or life-threatening or do not lead to hospitalization but may pose a substantial threat to the patient. Adverse events are also medically significant if they require intervention/treatment to prevent a condition which meets the criteria specified in the above definition for "serious adverse events".

Medically significant events must be reported like serious adverse events.

Examples of such events are intensive treatment in an emergency room or at home due to allergic bronchospasm, blood diseases or seizures which do not result in hospitalization, or the development of drug dependency or -abuse.

In addition, all suspected cases of the transmission of infectious germs (pathogenic and non-pathogenic germs) by a Pfizer product must be categorized as serious. The suspicion of this event is suggested if clinical symptoms or laboratory findings are present which indicate an infection in a patient who was exposed to a Pfizer product. In these cases, the wording "suspected transmission" and "transmission" must be treated as synonymous. These cases are categorized by pharmacovigilance personnel as unexpected and processed as a "serious case requiring immediate reporting." If applicable, these cases are additionally categorized as product defects.

Hospitalization

A hospitalization is defined as an inpatient admission (even if for fewer than 24 hours) to a hospital or equivalent healthcare institution or a prolongation of an existing hospital stay. Inpatient admission also includes transfer within a hospital to an acute/intensive care ward (e.g. from the psychiatric department to a general medicine department, from a general medicine department to a cardiac department, from a neurological department to a tuberculosis unit). An emergency room visit does not necessarily count as hospitalization. An event which results in a visit to the emergency room should however be assessed in terms of its medical significance

A hospitalization without a medical adverse event is not in itself an adverse event and must not be reported. Examples include:

- hospitalization due to a social indication (e.g. for homeless patients)
- hospitalization for administrative reasons (e.g. for an annual examination)
- Optional hospitalization which is not caused by an adverse event (e.g. for an elective cosmetic surgery)
- hospitalization for observation without a medical adverse event

- hospitalization for the treatment of a pre-existing illness which is not related to a new adverse event or the worsening of a pre-existing illness (e.g. for the diagnostic investigation of pre-existing abnormal laboratory values)
- Hospitalization required by the observational protocol during the study (e.g. for a procedure required in the observational protocol).

10.5.3. Scenarios which must be reported to Winicker Norimed within 24 hours

Below is an explanation for scenarios under which drug exposure occurs, including exposure

during pregnancy, exposure during lactation, medication errors, overdose, misuse, extravasation, and job-related exposure.

Exposure in utero

Exposure during pregnancy (also called exposure in utero [EIU]) occurs when:

- a woman under treatment with or when in direct contact with etanercept (e.g. environmental exposure) becomes pregnant or is found to be pregnant under these circumstances, or the woman following the discontinuation or after direct contact with etanercept becomes pregnant or is found to be pregnant under these circumstances (maternal exposure).

  An example of environmental exposure would be a case in which a pregnant woman comes into direct contact with Pfizer product: a nurse reports that she is pregnant and has come into contact with a chemotherapy product.

- a man had contact with etanercept due either to treatment or environmental exposure before or around the time of conception and/or during the pregnancy of his partner (paternal exposure)

Generally, all cases of exposure identified prospectively and retrospectively during pregnancy must be reported, regardless of whether or not an adverse event has occurred. Such instances of exposure must be reported like serious adverse events.

If a female study participant or partner of a study participant becomes or is pregnant during study treatment with etanercept, this information must be reported to Winicker Norimed using the NIS AE reporting form and the EDP supplemental form (EDP: *Eng. exposure during pregnancy*), regardless of whether an adverse event has occurred.

In addition, all information regarding environmental exposure with etanercept involving a pregnant woman must be submitted using the NIS AE reporting form and the EDP supplemental form. This must occur regardless of whether or not an AE has occurred (e.g. a female study participant reports that she is pregnant and has had contact with a cytotoxic product by inhalation or spillage).

The information submitted should include the expected delivery date (see information below on termination of pregnancy).

Follow-up will be performed to obtain general information about the pregnancy. Furthermore, follow-up observation will take place to gather information about the outcome of the exposure during pregnancy (EDP) for all EDP reports for which the outcome of the

pregnancy is unknown. A pregnancy will be tracked to the end or termination of the pregnancy (e.g. induced abortion) and Winicker Norimed will be informed of the outcome. This information will be reported as a follow-up to the initial EDP report. In the event of a live birth, the external integrity of the neonate at the time of birth may be evaluated. In the event of a termination, the reason/s for the termination should be stated and, if clinically possible, the integrity of the fetus evaluated by cursory visual inspection (unless the test findings before the termination conclusively show 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 death, neonatal death, or congenital anomaly [in case of a live birth, aborted fetus, intrauterine fetal death, or neonatal death]) the procedure for reporting SAEs must be followed.

Additional information on the pregnancy outcome reported as an SAE follow:

- Spontaneous abortion includes miscarriage and missed abortion;
- Neonatal deaths occurring within 1 month of birth should be reported as SAEs regardless of causality. In addition, infant deaths occurring after the age of 1 month should be reported as SAEs if the physician identifies or presumes a connection between the infant death and exposure with the investigational product.

Additional information regarding exposure in utero may be requested. Further tracking of the outcome of the birth will be handled on a case to case basis (e.g. tracking of premature infants to identify developmental delays).

In the event of the father being exposed, the study participant will be given the form for the release of information about the pregnant partner for his partner. It must be documented that the study participant has received this letter for his partner.

Exposure during lactation

Scenarios for exposure during lactation must be reported regardless of the presence of an associated AE. A report regarding exposure during lactation shall not be prepared if a medication from Pfizer approved specifically for use in lactating women (e.g. vitamins) is being administered in accordance with the approved indication. However, if the infant experiences an AE associated with the administration of such a medication, the AE is reported together with the exposure during lactation.

Medication error

A medication error is any accidental error with the prescription, dispensing, or administration of a product by healthcare professionals, patients, or users themselves, which may result in improper use or in injury to the patient.
Such events may be related to medical/pharmaceutical practice, the healthcare products themselves and with processes or systems, such as with the prescription, ordering, product information and labeling, packaging, product name and product description (nomenclature), composition of the medication, dispensing, sales, administration, training, monitoring, and use.

Medication errors include:

- Near-errors, regardless of whether a patient was directly affected or not (e.g. accidental/improper use i.e. accidental use of the product outside the approved indications or prescription by a healthcare professional or the patient/user)

- Confusion regarding the trade name (e.g. trade name, product name)

The physician must report the following medication errors to Winicker Norimed, regardless of whether a corresponding (serious) adverse event occurs:

- Medication errors with exposure of the patient to the drug, regardless of whether the medication error involves an AE or not

- Medication errors (including potential medication errors or near-errors) in which no patient is directly involved. If a medication error does not include the exposure of a patient to the drug, the following minimum criteria shall apply for a medication error report:

    - Identifiable reporter

    - Suspected drug

    - Medication error

Overdose, misuse, extravasation

Reports regarding overdose, misuse, and extravasation associated with a Pfizer product shall be reported to Winicker Norimed by the physician regardless of whether they involve an AE/SAE.

Lack of efficacy

Reports regarding a lack of efficacy from a Pfizer product shall be reported to Winicker Norimed by the physician regardless of whether they involve an AE/SAE and regardless of the indication for use of the Pfizer product.

Job-related exposure

Reports regarding job-related exposure with a Pfizer product shall be reported to Winicker Norimed by the physician regardless of whether they involve an AE/SAE.

10.6. Requirements for the reporting of claims and complaints for medical devices

All complaints for medical devices are documented on the corresponding pages of the CRF, regardless of whether they involve an adverse event. This includes potential near-incidents or the malfunction of a medical device if these are associated with the use of a medical device. A near incident or malfunction of the medical device is an event which could have resulted in death or severe health impairment or could result in death or severe health impairment should they recur.

The physician must notify Winicker Norimed of all complaints regarding medical devices within 24 hours of becoming aware of them.

11. COMMUNICATION AND PUBLICATION OF RESULTS

11.1. Publication plan

It is planned that 4 interim analyses will be performed and their results presented as an abstract at the appropriate national (DGRh) and international (EULAR, EADV, ACR) specialist conferences in 2015 and 2016. Formal interim reports are not envisaged. The final study results are then to be published in the 2nd half of 2017 in a German (Z Rheumatol) and 2 international journals (ARD, JEADV).

The final CSR is envisaged for June 2018.

11.2. Communication of safety problems

In the event of an imposed ban or imposed restriction (e.g. suspension of the study) from any competent authority, or if the treating physician becomes aware of new information which could influence the risk/benefit assessment for a Pfizer product, Pfizer should be informed immediately.

In addition, the treating physician will inform Pfizer of any measures s/he has taken to protect study patients from an immediate hazard to their health. S/he will also inform Pfizer

of all serious violations of the observational protocol for this non-interventional study of which s/he becomes aware.

12. **REFERENCES**

1. Bakker MF, Jacobs JW, Welsing PM, Vreugdenhil SA, van Booma-Frankfort C, Linn-Rasker SP, et al. Early clinical response to treatment predicts 5-year outcome in RA patients: follow-up results from the CAMERA study. Annals of the rheumatic diseases [2011]; 70(6): 1099-103.

2. Emery P, Breedveld F, van der Heijde D, Ferraccioli G, Dougados M, Robertson D, et al. Two-year clinical and radiographic results with combination etanercept-methotrexate therapy versus monotherapy in early rheumatoid arthritis: a two-year, double-blind, randomized study. Arthritis and rheumatism [2010]; 62(3): 674-82.

3. Klarenbeek NB, Guler-Yuksel M, van der Kooij SM, Han KH, Ronday HK, Kerstens PJ, et al. The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study. Annals of the rheumatic diseases [2011]; 70(6): 1039-46.

4. Kruger K, Wollenhaupt J, Albrecht K, Alten R, Backhaus M, Baerwald C, et al. [German 2012 guidelines for the sequential medical treatment of rheumatoid arthritis. Adapted EULAR recommendations and updated treatment algorithm]. Zeitschrift fur Rheumatologie [2012]; 71(7): 592-603.

5. Mease PJ. Measures of psoriatic arthritis. Arthritis care & research [2011]; 63 Suppl 11(S64-85.

6. Eder L, Chandran V, Shen H, Cook RJ, Gladman DD. Is ASDAS better than BASDAI as a measure of disease activity in axial psoriatic arthritis? Annals of the rheumatic diseases [2010]; 69(12): 2160-4.

7. Pathirana D, Ormerod AD, Saiag P, Smith C, Spuls PI, Nast A, et al. European S3-guidelines on the systemic treatment of psoriasis vulgaris. Journal of the European Academy of Dermatology and Venereology : JEADV [2009]; 23 Suppl 2(1-70.

8. Nast A, Boehncke WH, Mrowietz U, Ockenfels HM, Philipp S, Reich K, et al. [S3-guidelines for the treatment of psoriasis vulgaris Update 2011]. J Dtsch Dermatol Ges [2011]; 9(Suppl 2): S1-104.

9. Emery P, Breedveld FC, Hall S, Durez P, Chang DJ, Robertson D, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. Lancet [2008]; 372(9636): 375-82.

10. Strohal R, Puig L, Chouela E, Tsai TF, Melin J, Freundlich B, et al. The efficacy and safety of etanercept when used with as-needed adjunctive topical therapy in a randomised, double-blind study in subjects with moderate-to-severe psoriasis (the PRISTINE trial). The Journal of dermatological treatment [2013]; 24(3): 169-78.

11. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Annals of the rheumatic diseases [2014]; 73(3): 492-509.

12. Smolen JS, Landewe R, Breedveld FC, Dougados M, Emery P, Gaujoux-Viala C, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. Annals of the rheumatic diseases [2010]; 69(6): 964-75.

13. Kiltz U, Sieper J, Kellner H, Krause D, Rudwaleit M, Cheno JF, Stallmach A, Jaresch S, Braun J. Zeitschrift für Rheumatologie [2014]; Suppl. 2 (73): 78-96

14. Zink A, Strangfeld A, Schneider M, Herzer P, Hierse F, Stoyanova-Scholz M, et al. Effectiveness of tumor necrosis factor inhibitors in rheumatoid arthritis in an observational cohort study: comparison of patients according to their eligibility for major randomized clinical trials. Arthritis and rheumatism [2006]; 54(11): 3399-407.

13. **LIST OF TABLES**

Not applicable.

14. **LIST OF IMAGES**

Not applicable.

ANNEX 1. LIST OF STANDALONE STUDY DOCUMENTS

Not applicable.

ANNEX 2. ADDITIONAL INFORMATION

Not applicable.