RABBIT-SpA

Disease register for axial spondyloarthritis and psoriatic arthritis

Study Protocol

Dated July 22, 2016

1st Amendment February 25, 2020

Type of study	Prospective cohort study
Principal Investigators	PD Dr. Anne Regierer, PD Dr. Anja Strangfeld
Statistician	Anja Weiß, M.Sc.
Study coordination	Deutsches Rheuma-Forschungszentrum Berlin Programmbereich Epidemiologie Charitéplatz 1 10117 Berlin
Scientific advisory committee	Dr. Frank Behrens, Prof. Dr. Jürgen Braun, Dr. Joachim Listing, Prof. Dr. Georg Schett, Prof. Dr. Joachim Sieper
Pharmaceutical companies (as of January 1, 2020)	AbbVie Deutschland Amgen GmbH (Deutschland) Janssen-Cilag GmbH Lilly Deutschland GmbH MSD Sharp & Dohme GmbH Mylan Germany GmbH Novartis Pharma GmbH Pfizer Pharma GmbH UCB Pharma GmbH Further companies can access RABBIT-SpA if they are Marketing Authorization Holders for biologics, biosimilars or tsDMARDs licensed in Germany for the treatment of axSpA or PsA
Start of study	August 1st 2016
Follow-up	5-10 years individually
End of study	not determined

1. Background and general remarks

Axial spondyloarthritis (axSpA) and psoriatic arthritis (PsA) are the main diseases in the group of rheumatic conditions called spondyloarthritides (SpA). AxSpA itself comprises of ankylosing spondylitis (AS) and the newly defined subgroup non-radiographic axial SpA (nr-axSpA). The estimated prevalence rates are 0.8% for axSpA and 0.2% for PsA corresponding to about 550.000 axSpA patients and 140.000 PsA patients in Germany [1].

The treatment of axSpA and PsA has been revolutionized by the introduction of targeted therapies since 2003. Today, about half of the patients with ankylosing spondylitis (AS) treated in Germany by rheumatologists receive any of these drugs [2], in PsA the percentage is about 30% (DRFZ, unpublished data from the National Database, 2014). However, the safety and effectiveness of these newer treatments has not been sufficiently explored under real-life conditions so far. The various European registers have only rarely published results on this group of diseases. They mainly refer to drug survival and effectiveness. Comparing drug survival in axSpA, PsA and rheumatoid arthritis (RA), better retention rates compared to RA were found for both forms of spondyloarthritides in the Spanish [3] as well as in the Norwegian registers [4].

The British register reported high drug survival rates in PsA, even after failure of a first TNF inhibitor (TNFi) and switching to a second TNFi [5]. Clinical response and drug survival in PsA were also investigated by the Danish biologics register DANBIO showing lower response to the second TNFi after switching [6]. For PsA, a reduction in work disability after initiation of TNFi [7] and improvements in overall quality of life were shown [8].

In AS, most of the reports also pertain to drug survival and effectiveness: The Swedish register compared drug survival in a total of 2,520 patients with AS or undifferentiated spondyloarthritis and found better drug survival of the first TNFi in combination with csDMARDs [9]. The South Swedish register also found high drug survival rates on TNFi in patients with AS, specifically in males and those with peripheral arthritis [10]. The Finnish register reported equal effectiveness but better drug survival for etanercept and adalimumab compared to infliximab in 543 AS patients [11].

A recent Cochrane review found moderate to high quality evidence that anti-TNF agents improve clinical symptoms in the treatment of AS. The evidence concerning serious adverse events was limited to clinical trials with short duration. Using indirect comparative methodology inconclusive results have been found about differences between anti-TNF agents in terms of the key benefit or harm outcomes [12].

There is very limited real-life evidence concerning the safety of biologic and other targeted therapies in axSpA and PsA [13,14]. The British register BSRBR reported overall safety of TNF inhibitors in 596 PsA patients compared to seronegative RA [15]. The Swedish register ARTIS analysed lymphomas in patients with PsA or AS exposed to TNFi in comparison with the normal population [16].

In addition to these registers covering different rheumatologic diseases, some SpA specific registers/cohorts were established [17-20]. Publications from these registers are, however, limited and focus on the disease course in AS.

In summary, there are some reports on effectiveness but very limited information on the safety of biologic agents in axSpA and PsA. Importantly, nearly all reports lack adequate control groups so far. Furthermore, the development of new classification criteria for axial SpA in 2009 led also to the new diagnostic entity axial SpA which includes AS and the so-called non-radiographic axial SpA (nr-axSpA) [21,22]. Especially for the latter group of patients there is a strong need for valid data on the disease course and the long-term safety profile of applied treatments.

In contrast to axSpA and PsA, there is a wealth of information on targeted therapies in RA resulting from the different European biologics registers [23]. The close connection between features of the disease, the immunosuppressive properties of treatments, co-morbidity and various outcomes has been consistently shown. However, despite intensive research, many questions, specifically concerning high-risk patients and outcomes with long latency, remain to be answered even in RA. All the more this applies to axSpA and PsA: Due to large differences in the age and sex distribution, in risk factors, the spectrum of co-morbidities and co-medications, results on safety and effectiveness of treatments cannot be robustly transferred from RA to axSpA or PsA. Both disease entities of the group of spondyloarthritides have to be investigated separately since, for instance, risk factors and co-morbidities in PsA significantly differ from RA on the one hand and from axSpA on the other. In addition, benefits of treatment may be different from RA, e.g. due to NSAID reduction or improvements in work ability. Risks may be different due to other co-morbidities, specifically in PsA. Further, there is a specific lack of knowledge on the course of non-radiographic axSpA and the outcome of treatments.

The German biologics register RABBIT ("Rheumatoide Arthritis - Beobachtung der Biologika-Therapie") is among the largest biologics registers on RA in the world. It has been conducted as an independent long-term observational cohort study of the safety and effectiveness of biologic agents in RA since 2001. RABBIT-SpA, the disease register for axial spondyloarthritis and psoriatic arthritis, follows the concept of RABBIT. It is conducted as an open-ended, disease-specific prospective long-term observational cohort study. For methodological reasons, inclusion into the disease registry is linked to the start of a new treatment.

RABBIT-SpA observes patients treated with biologics, biosimilars, or other new targeted therapies licensed in Germany for the treatment of AS, nr-axSpA or PsA, together with conventional treatments. The respective current index drugs are listed on the project website *www.rabbit-spa.de*. In case of changes, this list will be updated immediately. The control therapies are all other conventional treatments for axSpA or PsA. The aim is to establish robust evidence on the long term outcomes of SpA, as well as effectiveness, long-term safety, and costs of the treatments under real-life conditions.

In order to ensure sustainable support for the conduct of the study, RABBIT-SpA is funded jointly by pharmaceutical companies with licensed biologic or other targeted agents for the treatment of axSpA or PsA. For that purpose, a joint contract has been made between the German Rheumatism Research Centre (Deutsches Rheuma Forschungszentrum DRFZ) and all funding companies. Further targeted therapies and the respective companies can access the study under the following conditions:

- the drug is licensed in Germany for the treatment of axSpA or PsA,
- the principal investigators, advisory board, and the pharmaceutical companies already funding RABBIT-SpA agree to include the new substance as index drug, whereby participation should not be denied without good reason,
- the pharmaceutical company responsible for the new drug accesses the existing contract and makes an appropriate contribution to the joint, unconditional grant for the study,

2. Aims of the study

Major aims are:

1. To describe the long-term effectiveness of treatment with targeted therapies, e.g. drug survival, effectiveness of treatment combinations, level of disease activity achieved.

2. To study the long-term safety of all available targeted therapies for axSpA and PsA

   This includes the observation of all adverse events (serious and non-serious) in order to assess the overall safety profile. Specific emphasis will be laid on "events of interest" (see 8.1.1 below).

3. To investigate the interplay between disease activity, comorbid conditions and safety outcomes, the interplay between disease activity, radiographic changes and functional outcomes and to explore the role of treatment in these interactions.

4. To describe selected direct and indirect costs of targeted therapies compared to standard therapy. This includes the description of health care consumption and work disability.

3. Study leadership and Scientific Advisory Committee

The scientific responsibility and study leadership is held by the German Rheumatism Research Centre Berlin, Programme Area Epidemiology, Pharmacoepidemiology Group (Head of Pharmacoepidemiology Group: PD Dr. Anja Strangfeld, Deputy Head of Pharmacoepidemiology Group: PD Dr. Anne Regierer). The principal investigators of RABBIT-SpA are PD Dr. Anne Regierer and PD Dr. Anja Strangfeld. The leading statistician is Anja Weiß. The responsibility of the study leadership comprises study design, data storing, data protection and security, monitoring, statistical analyses, preparation of reports, publication of results and representation of the study in the scientific community.

RABBIT-SpA has a Scientific Advisory Committee (SAC) which oversees the register. The SAC members are distinguished experts in the fields of axSpA and PsA. They are nominated by the study leadership in agreement with the sponsoring companies. A nomination period will be three years, re-nomination is possible. For the first three years the following persons were nominated and agreed: PD Dr. Frank Behrens, Frankfurt, Prof. Dr. Jürgen Braun, Herne, Dr. Joachim Listing, Berlin, Prof. Dr. Georg Schett, Erlangen, and Prof. Dr. Joachim Sieper, Berlin. Twice a year, joint meetings of the SAC, the study leadership and up to two (one substance under observation) or up to three representatives (>= two substances under observation) from the companies are held. In these meetings, the PIs report on the current state of the register and present future data analyses.

In order to pre-empt any conflict of interests, the members of the SAC do not receive any remuneration from the companies for their participation in RABBIT-SpA.

4. Study Design

RABBIT-SpA is a prospective observational cohort study. The rules of good pharmacoepidemiological practice are followed [24]. Physicians aiming at taking part in RABBIT-SpA must sign a contract with the DRFZ. The aim is to observe each patient for at least five years, if possible, for ten years.

Patients enrolled will have the following visits: baseline, months 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, 60. If the patient agrees, the observation will be prolonged with visits at 66, 72, 78, 84, 90, 96, 102, 108, 114 and 120 months.

There is no influence on any treatment decision from the principal investigators, scientific advisory board or pharmaceutical companies sponsoring the study. The type of the treatment administered, and the conduct of individual therapy is determined by the treating physician only.

5. Inclusion criteria

Inclusion criteria are:

- Signed informed consent
- Diagnosis of axial spondyloarthritis or psoriatic arthritis
- Age at inclusion >=18 years
- Cases: starting treatment with one of the index drugs
- Controls:
    - start of a new systemic standard therapy after failure of at least one systemic standard therapy (systemic standard therapy includes NSAIDs, csDMARDs)
    - clinically relevant increase in the NSAID dose

6. Assessments and evaluation methods

The following outcome measures will be investigated:

Effectiveness and cost components

1. Treatment survival and reasons for discontinuation
2. Course of the disease (e.g. change in disease activity parameters, function and general well-being)
3. Radiographic and MRI outcomes
4. Days in hospital
5. Medication, non-pharmacologic therapies and joint surgery
6. Days off work in employed patients
7. Early retirement and return to work (working days gained)

Safety

1. Occurrence of adverse events (serious/non-serious)
2. Outcome of pregnancy
3. Mortality

Flow chart of parameters investigated

	ax-SpA	**PsA**	**Study entry**	**At 3 months**	**Frequency of f/u**
Physician					
Inclusion criteria	x	x	x		
Demographics (year of birth, gender)	x	x	x		
Diagnosis/disease duration/1st symptoms	x	x	x		
Health insurance	x	x	x		
Diagnostic symptoms/ASAS criteria	x		x		
Chronic inflammatory back pain	x		x		
CASPAR-classification		x	x		
Type of PsA manifestation		x	x		Every 12 months
Imaging – radiographic findings	x	x	x		Every 12 months
Physician global disease activity	x	x	x	x	Every 6 months
Height	x	x	x		
Weight	x	x	x		Every 12 months
Extent (hip, waist)	x	x	x		Every12 months
CRP	x	x	x	x	Every 6 months

BSG		x	x	x	Every 6 months
HLA-B27	x	x	x		Every 12 months
RF / ACPA		x	x		Every 12 months
Lumbal lateralflexion	x		x		Every 12 months
Schober	x		x		Every 12 months
Arthritis (joint counts)	x	x	x	x	Every 6 months
Enthesitis	x	x	x	x	Every 6 months
Coxitis	x		x		
Joint replacements	x	x	x		Every 12 months
Vaccination	x	x	x		Every 12 months
Extraarticular manifestations	x	x	x	x	Every 6 months
Comorbidity/comedication	x	x	x		Every 12 months
Current therapy for SpA/PsA (systemic and topic)	x	x	x	x	Every 6 months
Glucocorticoids (systemic and local injections)	x	x	x	x	Every 6 months
Other therapies	x	x	x	x	Every 6 months
Previous therapies	x	x	x		
% body surface affected by psoriasis		x	x	x	Every 6 months
Pregnancy	x	x			Every 12 months
Adverse events	x	x		x	Every 6 months
Patient					
Patient global health status (NRS)	x	x	x	x	Every 6 months
Patient global disease activity (NRS)	x	x	x	x	Every 6 months
Sleep disturbances (NRS)	x	x	x	x	Every 6 months
BASDAI/BASFI	x		x	x	Every 6 months
ASAS HI	x		x		Every 12 months
HAQ/PSAID		x	x	x	Every 6 months
DLQI		x	x		Every 12 months
WHO-5	x	x	x		Every 12 months
PASS	x	x	x		Every 12 months
Patient satisfaction	x	x	x		Every 12 months
Smoking status	x	x	x		
Currently smoking	x	x	x		
Physical therapy	x	x	x		Every 12 months
Sport	x	x	x		Every 12 months
Level of education	x	x	x		
Work status	x	x	x		Every 12 months
Sick leave / Physician contacts / hospital admissions	x	x	x		Every 6 months
Work activity index (modified WAI)	x	x	x		Every 12 months
Adherence to prescribed medication	x	x	x		Every 12 months
Patient organisation	x	x	x		

Radiographs and MRIs will be uploaded at baseline and at follow-up, if available.

7. Adverse events

7.1. General procedures

Adverse events (AE) and serious adverse events (SAE) are recorded according to the ICH guideline on clinical safety data management: definitions and standards CPMP/ICH/377/95/E2A. Therefore, any

untoward medical occurrence observed in a patient has to be reported as AE. The AE does not necessarily have to have a causal relationship to the treatment of the patient. Any AE that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly/birth defect, or other medically important condition according to CPMP/ICH/377/95/E2A has to be reported as SAE. In addition, pregnancies have to be reported as serious adverse events. These definitions of AEs and SAEs are also provided in the CRFs. Physicians will be asked to appraise the possible causal relationship to drugs applied. Brand names need to be reported in the case of index drugs. Furthermore, physicians will grade all AEs in “mild”, “moderate” or “severe” according to the recommendations of the OMERACT Toxicity Working Group.

7.2 Events of interest

In agreement with all companies funding RABBIT-SpA, a number of “events of interest” which require specific attention were defined. They are:

- tuberculosis
- other serious infections (e.g. pneumonia, infections of the CNS, septicemia, bone or joint infections, opportunistic infections)
- congestive heart failure
- myocardial infarction
- stroke
- central demyelination
- serious hematologic disorders (e.g. bone marrow depression and hypoplastic anemia)
- neoplasms (lymphomas, solid malignancies, other neoplasms)
- serious systemic hypersensitivity reactions / serious infusion reactions
- hepatic failure
- serious gastrointestinal ulcer/perforation
- Crohn's disease
- colitis ulcerosa
- uveitis
- pregnancies
- deaths
- reversible posterior leucoencephalopathy syndrome (RPLS)
- renal failure
- progressive multifocal leukoencephalopathy
- Stevens Johnson syndrome (SJS) /toxic epidermal necrolysis (TEN)
- suicidal ideation/behavior
- interstitial lung disease (ILD)

Frequencies and crude incidence rates of these events of interest will be reported regularly (see 7.4). Changes of the list above have to be based on an agreement between the pharmaceutical companies funding RABBIT-SpA and the principal investigators.

7.3 Safety reporting

For all serious adverse events of interest, additional information, specific for the respective events, which is not part of the regular e-CRF is requested from the treating physician. Corresponding

queries will be generated automatically directly after saving the SAE of a patient into the RABBIT SpA database. Unique transaction keys will automatically be generated to allow an unambiguous assignment between SAEs reported in the e-CRF, automatically generated query forms, and possible additional medical reports with more detailed information on the SAE. Additional medical reports will be send by fax to the study center. The treating physician is responsible for data protection (e.g. to blacken personal data) in such cases. Additional information not part of the e-CRF is also requested for all other SAEs which are according to the assignment of the treating rheumatologist possibly related to an index or control treatment. SAEs with missing assignment of the causal relationship are considered as possibly related. The results of these queries are sent out to every company marketing the possibly related index drug. Additional information received for the control drugs are collected in the DRFZ.

The IT platform allows direct access to SAE queries and transfers these data into a separate SQL database in the study center. The SAE will be coded using the Medical Dictionary MedDRA from trained staff at the study center on the MedDRA preferred term level. Following the coding process the study center will send a first notification to the respective company of the index drug.

After receipt of the SAE specific query and, if available, the medical reports, the information in the separate SAE database will be completed and a second notification will be send to the respective company.

Documenting SAEs and related non-serious AEs on the physician report form does not release the treating physician from his/her responsibility to notify the Bundesamt für Arzneimittel und Medizinprodukte (BfArM) (German regulatory authority) or the Paul-Ehrlich-Institut of any adverse drug reactions in accordance with the professional code of conduct.

7.4 Six monthly reports

Every six months each pharmaceutical company funding RABBIT-SpA will receive a report which contains detailed records on each particular SAE (events of interest and other SAE) which occurred during the 6 months period and which were assigned to their index drug in the licensed indications covered by this registry. The report comprises also all SAEs assigned to control treatments. Except for deaths and malignancies an SAE is assigned to all index drugs a patient received during the last 3 months before the onset of the SAE (3-months risk window). SAEs which cannot be assigned to one of the index drugs according to this rule are assigned to control treatment. This approach with equal risk windows for different drugs will be used for feasibility reasons. In contrast, malignancies and deaths will be assigned to all treatments the patient was ever exposed to during the observation in RABBIT-SpA. The assignments are not connected with a conclusion about a causal relationship.

In addition to the detailed reports of SAEs the companies funding RABBIT-SpA will receive summary reports comprising crude cumulative incidence rates of events of interest and their 95% confidence intervals for their own drugs and for the control groups. The so called “Manchester template” is used to report the event rates. This “Manchester template” was defined and harmonized between the British, Swedish and German RABBIT biologics register and includes incidence rates of the total number of all observed SAEs.

Detailed multivariate analyses cannot be provided every six months, but will be done in scientific investigations and published in international journals.

Furthermore, summary reports of non-serious AEs assigned to an index drug of the company will be contained in the six months reports. If required by the respective company, these AEs will be grouped into mild, moderate, or severe AEs.

8. Statistical analysis

8.1. Safety endpoints

One aim of RABBIT-SpA is to protect future patients from harm caused by serious adverse events. It is impossible to achieve this aim by following a pre-specified list of primary hypotheses since the spectrum of possible SAEs is wide and every list would therefore be incomplete. New scientific results or new agents may lead to extensions and/or changes in the list of "events of interest". Therefore, the principal investigators and the study physician are free to decide which safety concern will be investigated next.

There is no general statistical analysis plan which would be appropriate for the different scientific questions. For different AEs different confounders have to be considered. Patients follow up for several years will likely receive changing treatments. These changes have to be taken into account. Furthermore, the decision to prescribe, to stop or to continue a treatment depends on the availability of treatment options and experiences with these alternatives. For this reason the mix of patients receiving a particular treatment may change during follow-up. The risk of developing an AE may therefore change over time for various reasons (see below). Possible confounding factors or biases have to be taken into account to avoid any false conclusion. In RABBIT-SpA this will be done by considering the following principles of statistical safety analyses:

Principles of the statistical analysis for publications

a) Confounding by indication will be taken into account

   Treatment decisions are based on the needs of a particular patient. Patients treated with new targeted therapies (index treatments) will be more severely ill and have more treatment failures than patients treated with standard therapies. For this reason comparisons based on crude unadjusted estimates cannot be interpreted adequately. In all publications from RABBIT-SpA appropriate statistical methods that are able to account for confounding by indication have to be applied.

b) Patient characteristics which likely influence the risk of developing a particular AE will be taken into account.

   Examples for these patient characteristics are age, sex, body mass index (e.g. for cardiac disorders), co-morbid conditions (e.g. COPD), treatment history of specific drugs (e.g. glucocorticoids or NSAIDs for cardiovascular events). In the first step those risk factors will be considered for which the increased risk was shown in previous studies. Further patient characteristics which possibly influence the risk of developing the AE will be investigated in addition.

c) The possible influence of co-medication will be considered.

   This applies especially, but is not limited to, treatment with glucocorticoids, NSAIDs and csDMARDs.

d) Changing risks over time will be considered. They may result from:

- Changes in treatment
- Selection processes caused by treatment decisions
- Attrition: Patients who remain on a drug for more than one year are likely different from the total sample of patients in whom the treatment with this drug was started.
- The course of the rheumatic disease itself
- The risk of developing an AE may be influenced by the inflammatory activity (e. g. the risk of developing atherosclerosis) or other disease-related factors

e) Power considerations needs to be conducted prior to the comparison of incidence rates

f) Appropriate statistical methods will be applied to deal with these challenges.

Examples are (fields of application in parentheses):

- Propensity score methods [25] (confounding by indication)
- Cox regression [26] (confounders, changing risks)
- Generalized regression models for survival data [27-29] (confounders, changing risks, recurrent AEs)
- Generalized estimation equations [30] (confounders, changing risks, recurrent AEs)
- Competing risk models [31] (competing risks, selection processes)
- Missing data models, imputation methods [32] (missing data).

g) In the case of rare events the advantages of nested case control studies will be taken into account.

With the availability of a large number of possible controls it should be possible to match cases who suffered from a particular SAE with controls who were similar to the cases according to a rather large number of possible confounders (up to 10).

h) The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline [33] as well as the EULAR points to consider [34] will be followed when results are published.

Furthermore, the results will be presented in a comprehensible way to enable the reader to follow them in detail. Papers published by the RABBIT team give examples how such analyses will be performed [35-44].

To support treatment decisions, the safety analyses will focus on investigations of the risk of individual patients rather than “average patients”. This approach therefore goes beyond the traditional approach in randomized clinical trials. Interactions between disease activity, risk factors of an individual patient and the treatments applied will be considered and relative and absolute risks will be calculated. One example for this kind of approach is the development of the RABBIT risk score for serious infections. For the diseases considered here an additional ascertainment of over the counter drugs (e.g. NSAIDs) and drug compliance is needed and for that reason included in the patient e-CRFs.

8.2 Effectiveness endpoints

Established endpoint measures in axSpA and PsA will be used to describe the long-term effectiveness of treatments. The principles described above for the analysis of safety endpoints will also be followed in a similar manner regarding effectiveness endpoints (for examples see [45-47].

One important outcome measure is work participation. It can already be addressed after enrolment of roughly 500 patients in the treatment and control groups each. Another one is the investigation of the influence of chronic changes on the one hand and disease activity on the other hand on the functional capacity and the quality of life of the patients. This also requires only a limited sample size but needs the data collection of radiographic and MRI data. RABBIT-SpA will further contribute to the ongoing discussion of the interaction between suppression of signs of inflammation, development of fatty lesions and chronic changes (syndesmophytes) in axSpA. These are only three examples of clinical and social outcomes which should be addressed with RABBIT-SpA.

8.3. Dropout analyses

In case patients are lost to follow-up, the reasons for study non-completion will be determined and comparisons of drop-outs and non-drop outs will be performed.

9. Informed consent / ethical considerations

The treating rheumatologists will recruit and enroll patients to RABBIT-SpA according to the inclusion criteria. Neither the DRFZ nor the companies will influence the treatment decisions taken by the physicians documenting the patients. They will inform the patients about the aims, the methods of data gathering and the scientific use of the data. Each patient will receive a written information leaflet. After having received the information, the patient will be asked to sign an informed consent (IC) form. It contains consent with the storage of pseudonymised data in the database and the use of anonymised data for publications. It will also explain the process of vital status research by the trustee. Further, pseudonymised data can be used for safety reporting to the companies. The signed IC form remains with the treating physician, the patient receives a copy.

The original study protocol dated July 22, 2016, was reviewed and approved by the Ethics Committee of the Charité Medical School in Berlin. This amendment and all further amendments will also be submitted to this Ethics Committee. Data will be archived for at least ten years after the end of the study at the DRFZ in Berlin. No selected data or entire data sets will be disclosed without authorization to third parties, including the companies, but the companies will receive upon request additional analyses on their own products separate from the joint evaluations. The study management, advisory board and companies will decide jointly whether data may be passed on for collaborative analysis (international studies).

10. Description of the IT system and the procedures of data collection

For data collection, the RABBIT-SpA online tool for physicians and patients will be used. It has been developed by Tembit Company (today: Serrala), Berlin, together with the DRFZ. The physician will sign a contract with the DRFZ and will then be authorized to use the system (Fig. 1). After informed consent, the physician will register the patient in the RABBIT-SpA database via a secure data connection (SSL) (Fig. 2). The physician will document the data in the practice or clinic while the patients can choose to use the online tool at home or in the practice/clinic. The patient questionnaires can also be printed out, filled out by the patients on paper and then typed into the

online system by the physician/study nurse in case the patient does not want to use the online system by him-/herself.

The pseudonymisation service (PSS) generates a unique pseudonym for each individual patient. After the physician has entered the diagnosis (axSpA or PsA), the respective questionnaires for physicians and patients are automatically provided. The patient receives an email with preliminary log-in data and can then log into RABBIT-SpA via an internet browser (Fig. 2). The preliminary password will need to be changed by the patient and the patients can then answer the first questionnaire.

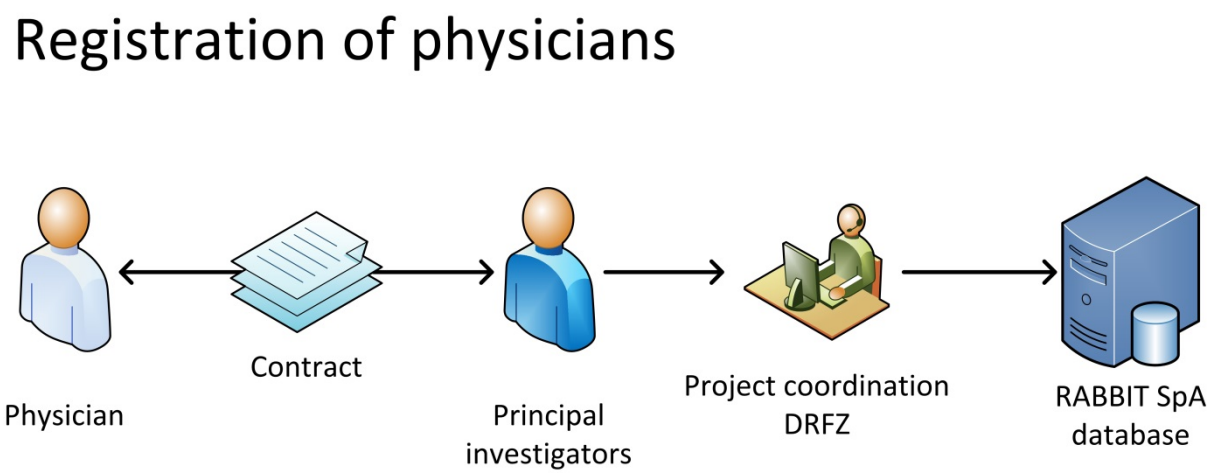

Figure 1: Registration of physicians

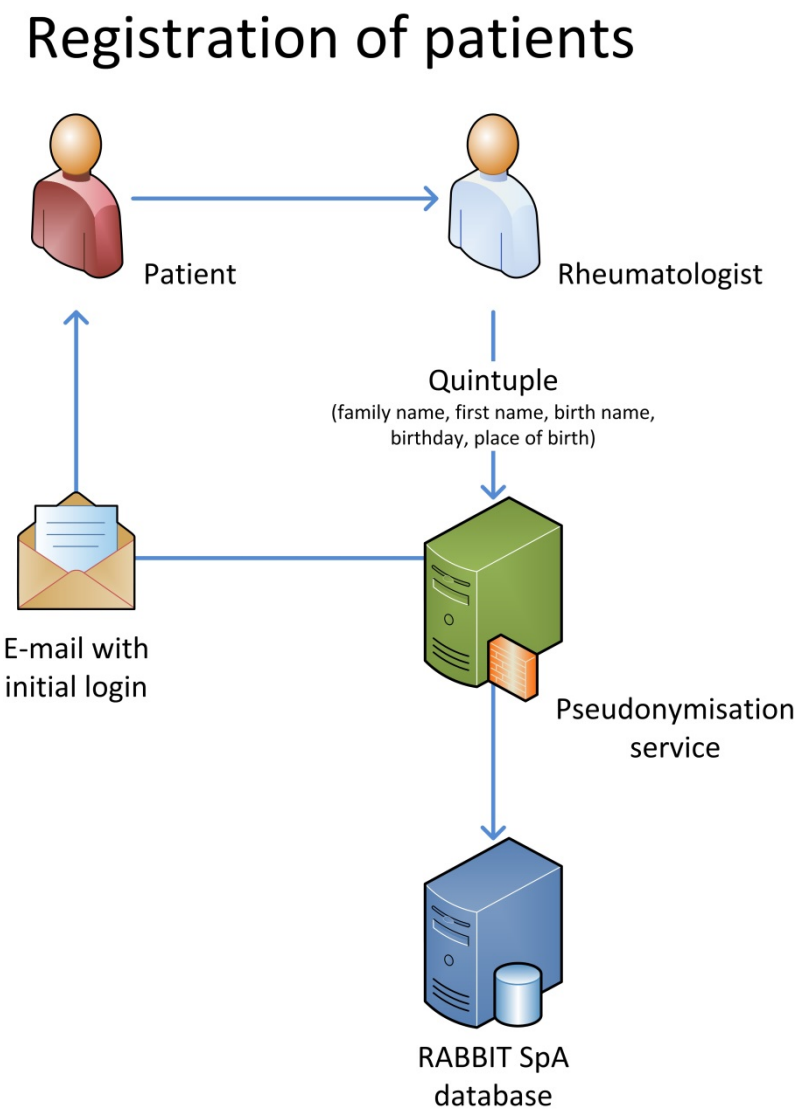

Figure 2: Registration of patients

At follow-up, the physician and patient log into the system and are provided with the questionnaires for the respective time points. In case the questionnaires are not answered in time, the physician and the patient are sent reminders.

The questionnaires can be completed with additional data (e.g. lab results) within a time period defined by the PIs. After this time period, the questionnaires are automatically transmitted.

11. Termination of study participation

The patients have the right to terminate study participation at any time point without giving reasons. In case a patient decides to terminate participation in RABBIT-SpA, the patients can unsubscribe either via their own profile or by informing their treating rheumatologist. They can decide whether they want to simply unsubscribe from RABBIT-SpA and terminate participation or whether they want to withdraw the informed consent. In this case, the personal data (name, first name, maiden name, date of birth and place of birth as well as postal address and e-mail) will be deleted and thus the data is fully anonymised.

12. Data protection

12.1 Role definition and access to the data

The collection, transfer, storage and analysis of the data follows the German data protection legislation. Only authorized personnel has access to the data after having given written agreement to observe the legislation concerning data protection, data security and confidentiality. The data are protected against unauthorized access and not transmitted to any third party.

Access to the data depends on individual roles. The following roles exist:

- Technical administration of database
- Trustee to re-identify a patient in case of death (DRFZ co-worker, not involved in RABBIT-SpA)
- Study leadership (PIs) and co-worker at the DRFZ
- Participating physician / study nurse
- Participating patient

The technical administration of the RABBIT-SpA application, the PSS and the database will be provided by Serrala Cloud Solutions GmbH (formerly Tembit Software GmbH) who will update the application or database, if necessary. Serrala has no access to the patient data. If necessary, staff from Serrala will be authorized by the PIs to get access to the RABBIT-SpA server. All work follows the four-eye principle. An authorized person at the DRFZ will receive limited, administrative access to the database in order to initialize the register.

As a matter of principle, the PIs and co-workers of RABBIT-SpA will have no access to patient identifying data such as last name, first name, date of birth or place of residence. They will use exclusively pseudonymised data for monitoring, data management and analysis.

The participating physicians and their authorized co-workers (study nurses) will have access to data entered by themselves. They see a list of their patients with names as well as a list of missing or incomplete questionnaires which they have to complete. After having submitted data, the physicians as well as the patients cannot change their data.

If no information has been received for at least two time points of follow-up the physician will be asked via the system by the DRFZ team whether the vital status of the patient is known. If the patient has died the physician is asked to report the date and cause of death to the study coordinating office. If no further information can be provided by the physician, the trustee will get special access to the system. This function is solely subject to the trustee role. The trustee will be able to re-identify the patient by receiving the name and address from the system. He will contact the patient to get information about the vital status. If this was unsuccessful, the trustee will contact authorities in order to establish the vital status of the patient. RABBIT-SpA will log every data entry of this process. RABBIT-SpA offers access to this respective patient exclusively for the trustee. The trustee is not allowed to get another user role in RABBIT-SpA. In case of death of the patient, the trustee will provide the gathered information via the system, i.e. in a pseudonymised way, to the study coordinating office.

12.2 Pseudonymisation

After having received informed consent, the physician registers the patient via a secure internet connection in the RABBIT-SpA database. The physician enters a quintuple, consisting of name, first name, maiden name, date of birth and place of birth as well as postal address and e-mail of the patient and the main diagnosis. The personal data are recorded in encrypted form. With the registration, an automatic encrypting program (pseudonymisation service, PSS) is started.

The PSS generates a pseudonym which does not allow any conclusions to be drawn as to the identity of the patient. The PSS contains a „fuzzy recognition tool“ for the automatic recognition of typos. The PSS also recognizes whether a patient is already registered in the RABBIT-SpA database and gives feedback. The PSS does not allow double registration of patients except in case of changing the treating rheumatologist. If the patient switches to a physician who already participates in RABBIT-SpA, the new physician enters the quintuple and thereby identifies the patient in the database. The patient confirms that this physician is authorized to enter data for RABBIT-SpA. The new physician gets access to the current questionnaires and the history of the physician and patient data but cannot change previous entries. If the new physician is not yet registered in RABBIT-SpA, he/she has to register first. The previous physician receives a message from the system and cannot access the data that are entered by the new physician.

The PSS in RABBIT-SpA was developed by Tembit Software GmbH (today: Serrala) according to the principles of the „Telematik Plattform“ as well as G3P Good Privacy Protection Practice in Clinical Research. It has been used in the framework of the BMBF funded project "SmartSenior" in 2012 and is currently used in the Rhekiss register. Both applications have been approved by the Ethics Committee of the Charité University Medicine Berlin.

12.3 Software and Server

The Rabbit-SpA Register is based on the internet application mdoc (mdoc=medical documentation system). The Rabbit-SpA Server is hosted by a certified provider (BSI, ISO27001) in Germany that guarantees an operation conform to German data protection legislation. Contemporary security measures protect the server reliably from external intrusions.

Rabbit-SpA access to Hospital Information Systems (HIS) or Practice Information Systems (PIS) is not intended.

Data are stored in a database on a server hosted by an authorized German provider. Patient related data are separated from clinical data. Patient related data (quintuple) are stored in encrypted manner. Based on the one-way-encryption SHA-256 (Secure Hash-Algorithm) there is no reference between the pseudonym and the patient data inside the database.

The selected host fulfills all requirements and provides all necessary certificates to store personal medical data conform to German data protection law.

13. Study procedures

Participating physicians will be provided with the study protocol, a contract with the DRFZ, information on the access to the e-CRF, precise instructions how to use the e-CRF, how to inform the patients and achieve informed consent, and support in the implementation of the study.

13.1 Queries

In case of (serious) adverse events and in case of implausible or missing data it will be necessary for the DRFZ to send queries to the treating physician. This will be done with a software aided process using the patient's pseudonym and a system generated unique “query number”. The rheumatologist will be informed about the query. The query (with full name of the patient) appears in his RABBIT-SpA profile. The physician can then answer the query in agreement with the data protection requirements.

13.2 Monitoring

The physician has access to the list of his patients and the open questionnaires. The study leadership decides about the period of validity of questionnaires. After this time period, the questionnaires will be auto-committed.

The patient will be regularly informed about new questionnaires in his RABBIT-SpA document center via email and asked to answer them.

The study leadership has access to a list that shows the current state of progress for all questionnaires for each participating rheumatologist. In addition, the modules have inbuilt plausibility checks in order to avoid implausible or missing data as far as possible.

14. Expected numbers of enrolled patients

To achieve the aims of RABBIT-SpA, the team at the DRFZ will take several measures to motivate rheumatologists to enroll patients into RABBIT-SpA. However, since RABBIT-SpA is an observational study of routine rheumatologic care in Germany, the number of patients under a particular drug who will be enrolled is not manageable by the study centre. Nevertheless, we aim at enrolling at least 500 patients under each of the index drugs until end of 2019 plus two control cohorts (axSpA and PsA) of 1000 patients each.

15. Personnel

A study physician will be responsible for the study supervision, coding adverse events and compiling reports. A statistician will be responsible for the data analysis and statistical testing. Medical data managers will be responsible for study monitoring (organization of schedules, coding, dropout research, etc.). The medical data managers continuously monitor the e-CRFs and issue queries in case of incomplete or implausible information.

16. Cost sharing among companies

All companies participating in RABBIT-SpA support the register with a contribution to the joint grant. Independence of the principle investigators is guaranteed by the main contract that involves all parties.

Each company has an equal share of the costs at the DRFZ and the Rheumatologische Fortbildungsakademie (RhAK). Those companies who have one agent under observation will have a share of 1 part, for every additional agent 0.5 parts will be added. The budget is set up in advance for one or more years by the DRFZ. Identical contracts are then sent out by the DRFZ to all companies and signed by the DRFZ, the RhAk, and the individual companies. In addition, the work load of the participating rheumatologists will be compensated for with amounts of money that correspond with the regulations of the “Gebührenordnung für Ärzte”.

The documentation fees for the participating rheumatologists will be as follows:

Baseline visit with patient information about the aims and procedures of RABBIT-SpA, written informed consent, notification of the patient to the system, gathering clinical and lab data and filling the e-CRF, estimated time: 65 minutes	75 EUR
For each follow-up visit (estimated time: 45 minutes)	50 EUR
Answers to SAEs (specific information on SAE)	30 EUR
Additional provision of medical reports	20 EUR
Upload of MRI / radiographs	25 EUR

The documentation fees are summed up in the beginning of each year for the previous year. Each company covers the documentation fee for patients treated with their own drug plus an equal share of the fees for the control groups. This treatment assignment will be determined once a year. The queries concerning serious adverse events are covered by the company who receives the report. If more than one drug was given in the considered time span, all companies involved receive the report. These costs are then splitted among these companies. Costs for SAE queries of the non-index drugs of the control group are equally shared among all companies.

The documentation fees are paid to the physicians by the RhAK. The participating rheumatologists will receive payment once a year for the preceding year. In order to enable the RhAK to pay the documentation fees to the participating rheumatologists on time in the beginning of each year, the companies perform payment in advance of 90% of the expected sum by January 15th of each year for the preceding year. The RhAK receives a handling fee which is agreed upon among all companies.

17. Publications

The results will be evaluated and published by the PIs on a regular basis. It is planned to publish analyses in high ranked international journals as well as to present the results at national and international congresses, such as the annual meeting of the German Society of Rheumatology, the annual EULAR meeting, and the annual ACR meeting. The names of all participating doctors who have brought in at least 2% of the number of cases will appear in the acknowledgements of the publications. Rheumatologists with a particularly high involvement can be co-authors. On an individual basis, the study leadership and the SAC will together decide on the question of co-authorship. The financial support of the manufacturers is also acknowledged in publications.

The companies are entitled to use the results of the semi-annual reports for their own purposes. This includes internal use for reports and presentations. If data shall be published, the source has to be given and the rules for approval by the other parties as outlined below will apply also in these cases. The right to publish original data first remains with the DRFZ.

Before being submitted for publication (to a publishing house or to any other form of media), all publications must be approved by the parties. In case of full publications, each party has a period of 30 days, in which it can object, starting on the date on which the proposed publication is received from another party. Objections must be made in writing and addressed to the DRFZ. If no objection is raised during such time, approval is deemed given. If an objection is raised regarding the contents of a publication within these 30 days, and if, subsequently, the matter is not resolved, the party raising the objection has the right to add a written statement in the form of a footnote or some other suitable form to the publication in question. If this written statement is not received by the party responsible for arranging the publication within a period of 30 days after the objection was initially

raised, the latter Party shall be entitled to proceed with the publication without the statement. In case of abstracts for scientific congresses, each party has a period of 14 days in which it can object, starting on the day on which the proposed abstract is received.

18. Additional investigations

In principle, it is possible for sub samples of subjects to be included in supplementary investigations (e.g. basic scientific blood and tissue tests). Besides a separate clarification of any ethical and data protection issues, and besides the patients' informed consent, any such inclusion in supplementary investigations shall require the prior agreement of the study leadership and the advisory committee. All such supplementary studies shall require independent organisation and financing.

19. International collaboration

It is envisaged to embed RABBIT-SpA into the international collaboration of biologics registers, set up under the umbrella of EULAR. Harmonisation of items in the e-CRF with other registers collecting data on axSpA and PsA as well as with the German Psoriasis register "PsoBest" will allow to address clinical questions and to investigate very rare outcomes that are beyond the scope of individual national registers. In RABBIT-RA we have already shown that this is possible. Together with the British Society for Rheumatology Biologics Register, our group has been leading the first two joint data analyses of European biologics registers on lymphomas and malignant melanomas [48].

Berlin, 25. 2. 20

PD Dr. Anne Regierer	PD Dr. Anja Strangfeld	Anja Weiß, M.Sc.

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