# Primary and secondary patient data in contrast: the use of observational studies like RABBIT

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## ABSTRACT

*The study of secondary patient data, particularly represented by claims data, has increased in recent years. The strength of this approach involves easy access to data that have been generated for administrative purposes. By contrast, collection of primary data for research is time-consuming and may therefore appear outdated. Both administrative data and data collected prospectively in clinical care can address similar research questions concerning effectiveness and safety of treatments. Therefore, why should we invest the precious time of rheumatologists to generate primary patient data?*

*This article will outline some features of primary patient data collection illustrated by the German biologics register RABBIT (**R**heumatoid **a**rthritis: o**b**servation of **bi**ologic **t**herapy). RABBIT is a long-term observational cohort study that was initiated more than 15 years ago. We will discuss as quality indicators: (i) study design, (ii) type of documentation, standardisation of (iii) clinical and (iv) safety data, (v) monitoring of the longitudinal follow-up, (vi) losses to follow-up as well as (vii) the possibilities to link the data base. The impact of these features on interpretation and validity of results is illustrated using recent publications.*

*We conclude that high quality and completeness of data prospectively-collected offers many advantages over large quantities of non-standardised data collected in an unsupervised manner. We expect the enthusiasm about the use of secondary patient data to decline with more awareness of their methodological limitations while studies with primary patient data like RABBIT will maintain and broaden their impact on daily clinical practice.*

## Introduction

There are two principally different approaches to assess the safety and effectiveness of therapies in routine clinical care: the hypothesis-driven generation of primary data or the use of secondary data such as health records or claims data for research purposes. The use of claims data bases has increased in recent years. Both approaches have advantages and disadvantages. We would like to outline specific differences and delineate why well-designed prospective observational cohort studies will remain essential to get a full and unbiased picture of the benefits and harms of treatments.

In 2015, first results of the American College of Rheumatology (ACR) project RISE (***R***heumatology ***I***nformatics ***S***ystem for ***E***ffectiveness) (1) were presented at the ACR congress. In this impressive project almost 240,000 patients were registered in one year only, including 60,000 patients with rheumatoid arthritis (RA). The success of this project is not restricted to the number of patients, it is determined by creating a platform that extracts patient data from most electronic systems used for the documentation in daily care in the US. The primary aims of RISE are to investigate markers for quality of care and effectiveness of treatment. Similar to RISE, studies based on claims data make secondary use of patient data that were generated initially for administrative purposes. The methods to examine these data sources have improved significantly in recent years and algorithms applied to validate diagnoses generate relevant results regarding the safety of different treatments (2).

In the light of these developments, the need for studies that were designed to answer specific research questions by generating and analysing primary patient data might appear debatable. Long-term observational studies of patients in daily practice were already initiated in the 1980s in rheumatology (3-5). Their development was accelerated as a consequence of the advent of biologic

disease-modifying antirheumatic drug therapies (bDMARDs). Very promising results from randomised controlled trials (RCT) suggested a considerable deceleration or even arrested joint destruction in RA patients. However, several uncertainties and concerns were raised regarding the long-term safety of biologic agents. Therefore, extensive research efforts resulted from the interest of clinicians, drug manufacturers, regulators and not least health insurances in initiation of several long-term observational studies. Some of these studies were extension studies of RCTs (6, 7). More general approaches comprised all available bDMARDs for the treatment of RA. Several disease registries were established in Europe more than 15 years ago to characterise the use of biologic agents in real-world patients with RA (8-10).

Since then disease registers adopted new developments in information technology. The Danish and the Portuguese registers managed to switch the type of documentation from paper- to electronic documentation (11, 12); in the Danish register also standard data of electronic health records (EHR) are accessible. Others like the Swedish register used electronic health records directly from start. Nonetheless, some register documentation has remained paper-based until today. Therefore, considerable differences regarding the type of documentation, study design and the reporting of adverse events (AE) can be found nowadays across registries. However, they generally are similar in the generation of primary data to address the specific questions of long-term safety and effectiveness of RA treatments.

In Germany, the RABBIT study (***R***heumatoid ***a***rthritis: o***b***servation of ***bi***ologic ***t***herapy) was initiated in 2001. The purpose of RABBIT is the investigation of drug effects caused by bDMARDs compared to conventional synthetic (cs)DMARDs. To some extent, the design of RABBIT resembles RCTs with pre-specified follow-up visits and enrollment of patients with the start of a bDMARD treatment or – in the control group – a csDMARD after at least one csDMARD failure.

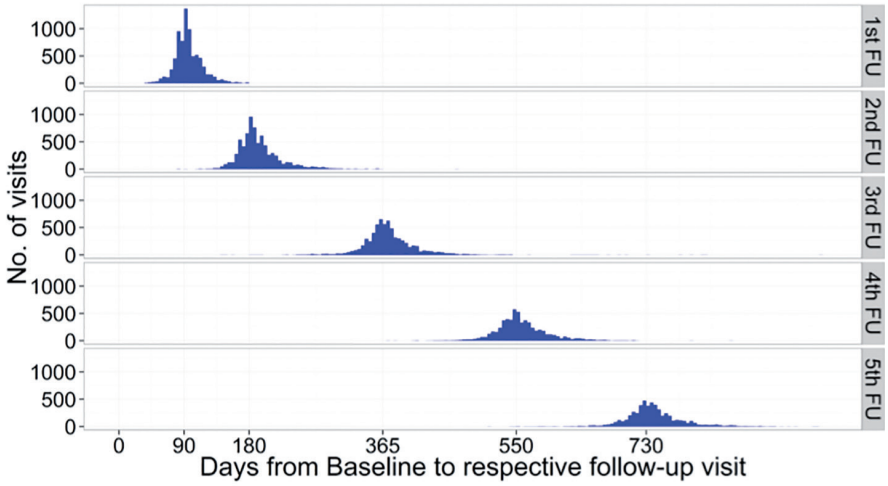


**Fig. 1.** Adherence to scheduled study visits.
The figure illustrates histograms of the difference in days between enrolment and the respective study visit. No.: number; FU: follow-up.

Since its start, the RABBIT study underwent some modifications although major aspects of the study design have been retained since 2001. One of the principles is the paper-based documentation which may cause RABBIT to appear as a historical remnant. However, given the clinical routine of rheumatologists in Germany and patient preferences concerning documentation of data such a judgement might be too hasty. This article reviews pros and cons of RABBIT concerning study design, documentation of data, enrolment restrictions, monitoring of follow-up, reporting of (serious) (S)AEs and will illuminate those data and results that cannot be captured by a secondary use of EHR data.

## Study design

All adult RA patients meeting the ACR criteria of 1987 (13) with an age at onset of ≥16 can be enrolled in RABBIT with the start of a csDMARD after failure of at least one csDMARD or with the start of a biologic agent. Patients are assigned to (a) the control group of csDMARDs or (b) a bDMARD or biosimilar group. No further inclusion criteria and no exclusion criteria are applied.

The restriction that patients can only be enrolled at start of a new treatment resembles the design of RCTs and implies that baseline data reflect pre-treatment status which is crucial for all analyses of effectiveness. Nonetheless, the restriction to enroll patients with a csDMARD treatment only after at least one csDMARD failure implies also a selection of more severely affected RA patients: those patients who do well on their first csDMARD, which is nowadays most often methotrexate, are not represented in RABBIT.

The observation of each patient is intended for at least five years, and can be extended up to ten years after additional informed consent of the patients. The follow-up visits after enrollment (baseline) are pre-specified: at month 3 and 6, and then every 6 months. The exact dates of the follow-up visits are specified for each patient at enrollment. To encourage the adherence to scheduled visits the rheumatologist is notified of an upcoming study visit. However, deviations from scheduled visits are accepted.

In general, notification of rheumatologists of upcoming patient visits provides considerable benefits. Most patients adhere to the study design of follow-ups (Fig. 1) and can be compared at very similar time points after initiation of a particular DMARD.

## Data collection in RABBIT

*Type of documentation*

The documentation in RABBIT is paper-based. Rheumatologists and patients complete standardised and anonymised questionnaires which are sent to the German Rheumatism Research Center via fax. Checks of data plausibility are therefore not out-

sourced to the rheumatologist or patient by electronical means; they are completely applied in the study center of RABBIT. Inquiries to rheumatologists are necessary for 30% of physician questionnaires, which is very time consuming and requires a large staff. On the other hand, this type of documentation means that reporting data of a routine follow-up visit by a rheumatologist requires only approximately five minutes and is independent of a technical device.

The major drawbacks of this type of documentation is the delayed entering of questionnaire data into the database, no availability of the history of patients' disease activity in the concurrent consultation between patient and physician and no awareness of all patient-reported outcomes.

Nevertheless, acceptance of paper-based documentation remains very high (Fig. 2). In particular, some elderly patients as well as a considerable proportion of physicians prefer not to use electronic devices.

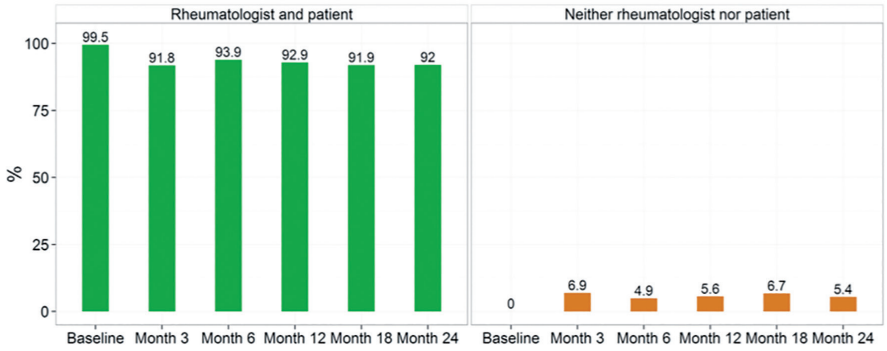


**Fig. 2.** Response rates of rheumatologists and patients*.
*Considered were patients under observation for at least two years. Questionnaires from both the rheumatologist and the patient are available in more than 90% of the scheduled study visits (left panel). The percentage of study visits with no questionnaires at all is very low (right panel). The discrepancy between the left and right panel represent questionnaires of rheumatologist or patient only.

*Documentation of clinical data*

The reporting of clinical data and patient-reported outcomes differs between the baseline visit and follow-up visits. At baseline, rheumatologists as well as patients fill in the most comprehensive questionnaire. The core set of items presented to the rheumatologist comprises current treatment with DMARDs, glucocorticoids or nonsteroidal anti-inflammatory drugs, laboratory markers of erythrocyte sedimentation rate, C-reactive protein, rheumatoid factor, as well as tender and swollen joint counts. In addition to the core set, rheumatologists report on 24 predefined comorbidities including their medical treatment, two free-text lines to report other comorbidities and previous treatment courses with csDMARDs and bDMARDs prior to enrollment. The latter encompasses start and stop dates as well as reasons for discontinuation.

The core set of outcomes presented to patients comprises: patient global assessment of disease activity, fatigue, pain, quality of sleeping, number of hospitalisations and physician visits as well as physical function (Funktionsfragebogen Hannover), a German instrument similar to the Health Assessment Questionnaire (14). This core set of the patient questionnaire is augmented at baseline and at annual visits with a quality of life measure (SF-36) (15), smoking habits and employment status.

*Documentation of safety data*

At every point of follow-up, the rheumatologist is asked to report any (S)AE as free text irrespective of the actual treatment. As part of the standardised questionnaire, the event date and a gradation (mild, moderate, or severe) are recorded (16). Assessment of a causal relationship with the prescribed drug is requested, defined as definite, probable, possible, unlikely, unrelated, or unknown. Events are classified as serious or non-serious by the rheumatologist according to the International Conference on Harmonisation E2A guidelines (17). A total of 42,918 AEs were reported until October 31st, 2015, of which 11,319 were SAEs. No information was available about the severity of 75 (0.17%) events. Besides physician reported events, patients additionally report all health impairments that occurred since last follow-up (18). The management of (S)AEs is detached from the regular quality assessment of questionnaires. Data input is conducted by three distinct medical data managers trained for standardised documentation. In this process, all events are checked and coded supervised by a physician using the preferred term level of the Medical Dictionary for Regulatory Affairs (19). If a patient was treated with a bDMARD at the time of the SAE, the manufacturer receives notification about this event via E-Mail within 24h after reporting. For fourteen previously defined events of interest (Table I), the reporting rheumatologist uses standardised queries. Event specific questions include diagnostic details, therapies, and outcome, *e.g.* regarding serious infection the exact diagnosis, localisation, microbiology, serology, and therapy are inquired. For events requiring hospitalisation, the rheumatologist is asked to provide a discharge letter. As an example: of 124 malignancies reported until December 2006, further information was not available in only five patients. In 50% of the cases, hospital discharge letters with the exact histopathologic results were sent to the register (20).

Unclear cases and open questions are discussed with the lead study physician on a regular basis. Analyses of (S)AEs always are preceded by a verification of events. Depending on the outcome, external validations also are applied by (a) inviting experts in their respective fields to conduct event validation (21) or (b) by performing on-site visits at the respective rheumatologists to review patients records (22).

## Quality of the data

The quality of data from longitudinal observational studies can be impaired by missing data in covariates of patients under observation, by imprecision of data referring to AEs, by high

**Table I.** Diagnoses defined as events of special interest.

| | |
|---|---|
| Death | Malignancies |
| Demyelination in the central nervous system | Myocardial infarction |
| Gastrointestinal perforation | Pregnancy/Birth outcome |
| Heart failure | Refractory anaemia/Pancytopenia |
| Infusion reaction/Hypersensitivity reaction | Serious infections (Tuberculosis excluded) |
| Liver failure | Stroke/Transient ischaemic attacks |
| Lymphoma | Tuberculosis |

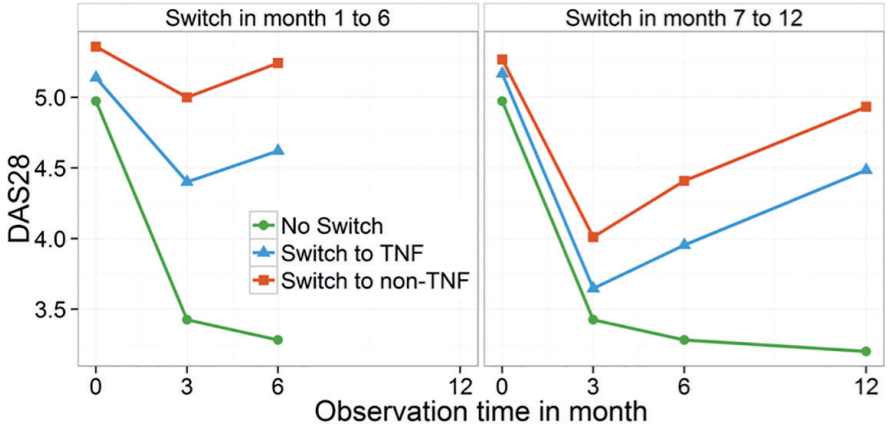


**Fig. 3.** Mean values of the DAS28 of biologic-naïve patients enrolled with the 1st TNFi within the first 6 (12) month of follow-up.
Patients were stratified according to a switch to another bDMARD or the continuation of the 1st TNFi.

dropout rates or by systematic loss of specific patient groups. However, also the design of a study is crucial. While the impact of missing data, uncertainties in diagnoses and systematic loss of patients are self-explanatory regarding the quality of data, the relevance of the design of a study is less frequently discussed.

Regular follow-ups like in the British register BSRBR (8) or RABBIT may appear as a restriction or dictation to rheumatologist, but they are beneficial to investigate study aims. Standardised follow-up intervals create an independence of available data from consultations while spontaneous patient visits are often driven by disease activity or AEs. Patients doing well on a particular treatment will be less likely to arrange an appointment at the rheumatologist which results in less frequently documented data. To examine associations of time-varying disease activity and the occurrence of AEs, months or years after enrollment, it is crucial to have the disease activity available in patients with and without the AE. By contrast, if patient visits follow clinical routine, the researcher may either make assumptions about patients with less frequent study visits, most often data are assumed to be unchanged since the last visit, or restrict the analyses to patients with available data, which automatically selects patients with higher health care utilisation.

The usefulness of regular follow-ups can be illustrated with the research question of an optimal treatment algorithm in patients that inadequately responded to 1st-line tumor necrosis factor α inhibitors (TNFi). Several observational studies investigated whether 2nd-line use of TNFi is appropriate or a switch to rituximab should be preferred (23-25). Notably, in all these studies, patients who switched to a 2nd TNFi had significantly lower values of the DAS28 at baseline compared to patients that switched to rituximab after 1st TNFi. This common peculiarity indicated a systematic difference in the selection of the 2nd bDMARD in real-world patients with RA. One hypothesis is that a different mode of action is preferred in RA patients who have no response to the 1st TNFi. This hypothesis was investigated in biologic-naïve patients enrolled in RABBIT with the 1st TNFi and who were followed for 12 months (Fig. 3).

Due to the adherence to regular study visits (Fig. 1), there is no dependency of patients' disease activity on available data: patients doing well on a particular treatment also contribute data on their disease activity. Regular follow-ups are therefore beneficial to investigate time-varying effects and to detect selection preferences of a treatment. Regarding the choice of a 2nd bDMARD, patients with no response to the 1st TNFi (Fig. 3, left panel) or a complete secondary loss of effectiveness (Fig. 3, right panel) were more likely to be switched to a non-TNFi. Patients with a moderate but insufficient response to the 1st TNFi were more likely to be switched to a 2nd TNFi. Interestingly, this preference appears to be common across European observational studies (23-25) and results in significantly lower disease activity of patients enrolled with a 2nd TNFi than those on a biologic agent with another mode of action.

### Linking to external data bases

The performance of a register is often also assessed by the capability to link the data to external reference data bases. The advantages of linkage are that (i) additional patient level information may be added to the analyses, (ii) linkage may reveal underreporting or inadequate classification of AEs like malignancies and (iii) linkage can reduce register efforts in the documentation of SAEs.

However, it is often unrecognised that linkage of different data bases is not free of risks to introduce bias (26-28): unambiguous patient identifiers or extensive algorithms to match units of observation are required to gain the desired advantages of linkage. Therefore, the standards of reporting and documentation in each of the data bases must be very high.

In Germany, data protection regulations preclude almost any linkage even for research and in this matter the RABBIT study is limited in evaluating underreporting or appropriate classification of AEs. However, investigation of causes

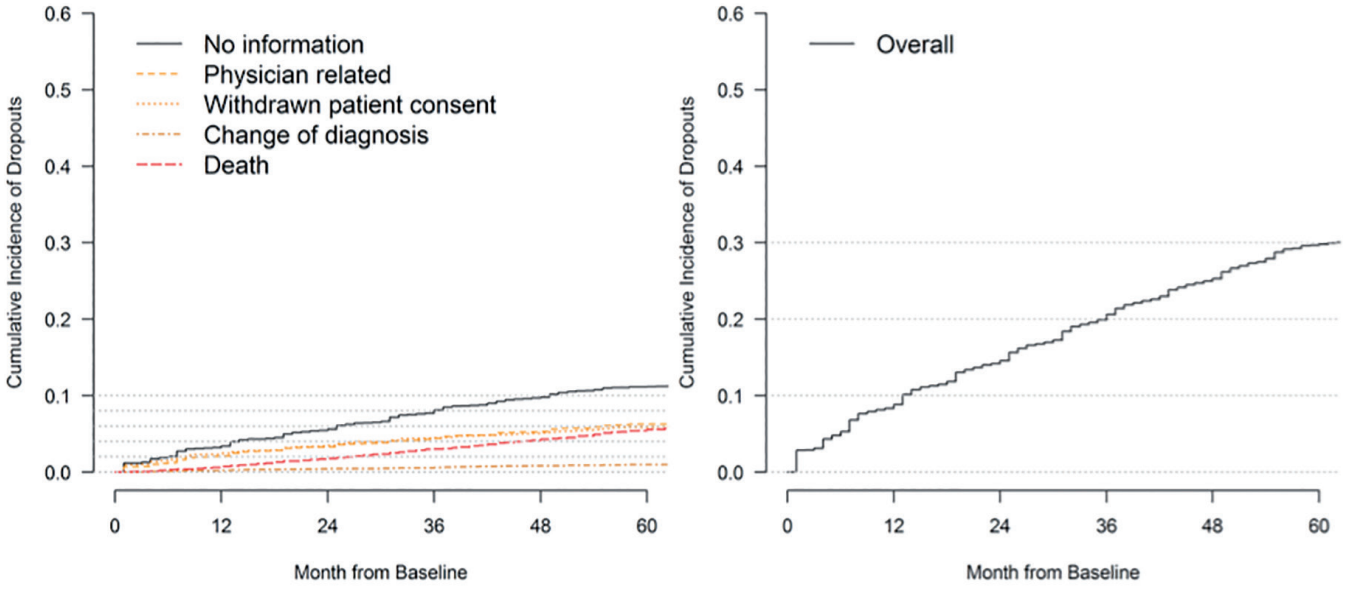


**Fig. 4.** Cumulative incidence of attrition.
In the left panel, cause-specific cumulative incidence and in the right panel, the overall rate of attrition over 5 years of follow-up.

of death is not affected by this limitation.

**Loss to follow-up**

In the monitoring of RABBIT, a specific routine has been implemented to investigate causes of drop out. It starts for all patients not visiting the rheumatologist at two consecutive follow-ups. In this case, (1) the rheumatologist is queried regarding patient status. If no information can be provided by the rheumatologist (2) the patient and its relatives are contacted. These two measures already generate valuable information regarding patients' status, some rheumatologist report non-compliance of a patient and some patients withdraw their consent to continue follow-up. In either case, drop out due to death can be precluded. If none of the measures is successful (3) local administration offices are contacted to gather information on patients' survival or change of residence. In case a patient has died, death certificates are requested and causes of death are investigated. These standard routines are very time-consuming but in the end successful: in 95% of all deaths occurring during observation information on the cause of death is obtained (29). All these measures are covered by patients' informed consent.

The overall drop-out rate in RABBIT is approximately 6% per annum; in less than 3% the reason for discontinuation is unknown but most probably not due to death (Fig. 4).

**The development of RABBIT in 15 years**

The enrolment of patients in RABBIT started in 2001 with the first two TNF inhibitors and a control group of patients on csDMARDs. From 2003 onwards patients could be enrolled also with adalimumab or anakinra. In 2007 and 2008 only patients treated with abatacept or rituximab were enrolled, the recruitment on all other DMARDs was paused. Since 2009 patients starting csDMARDs, bDMARDs or (since 2015) biosimilars can be enrolled. Table II shows how patient characteristics changed over time, reflecting earlier and broader use of biologic agents. Patients recruited in more recent years are older, have shorter disease duration, lower DAS28 at baseline, better function and lower numbers of previous DMARD failures and of unfavorable prognostic factors.

**Funding and academic freedom**

It is crucial to guarantee the long-term future of RABBIT. The register is sponsored by all pharmaceutical companies which market biologic agents or biosimilars licensed for the treatment of rheumatoid arthritis. All companies have signed one joint contract, defining equal rights and duties. If a company decides to leave the register, it will further support RABBIT for another five years in order to ensure such individual follow-up time for all patients. This long-term commitment extends far beyond the possibilities of public funding. The principal investigators of RABBIT have full academic freedom. Sponsors have no influence on data collection, processing or evaluation, and no access to the database itself. They receive semiannual reports on SAEs that have occurred under their drug or in the control group. Every six months, meetings are held with representatives of the funding companies, the scientific advisory board (four rheumatologists) and the principal investigators (PIs).

RABBIT is supported by a joint, unconditional grant from all pharmaceutical companies holding a marketing authorisation for biologic drugs used in RA including: AbbVie, Bristol-Myers Squibb, Celltrion, MSD, Sharp & Dohme, Pfizer, Roche, Samsung, and UCB.

**Discussion**

This article reviews characteristics of the observational study RABBIT that was designed and initiated 15 years ago to investigate the effects of bDMARDs in comparison to csDMARDs in patients with RA. On the one hand,

**Table II.** Baseline characteristics of patients enrolled into the RABBIT register stratified by time of enrolment and therapy (bDMARD or csDMARD).

| | Enrolment period | | | | |
|---|---|---|---|---|---|
| | 2001-2003 | 2004-2006 | 2007-2008 | 2009-2012 | 2013-2015 |
| | Enrollment therapy: bDMARD | | | | |
| N | 1,179 | 2,182 | 917 | 3,418 | 1,882 |
| Female gender, n. (%) | 901 (76.4) | 1730 (79.3) | 724 (79) | 2592 (75.8) | 1403 (74.5) |
| Age in years | 53.6 (12.5) | 53.9 (12.2) | 56.7 (12.4) | 56.7 (12.6) | 56.8 (12.8) |
| Disease duration in years | 12.0 (9.4) | 11.6 (9.4) | 14.3 (9.9) | 10.9 (9.1) | 10.2 (9.0) |
| DAS28 | 6.0 (1.2) | 5.6 (1.3) | 5.5 (1.2) | 5.1 (1.3) | 4.9 (1.3) |
| Physical function (%)[#] | 53.6 (23.1) | 58.8 (22.6) | 51.3 (22.7) | 63.5 (23.2) | 65.8 (23.1) |
| No. previous csDMARDs | 3.7 (1.5) | 3.2 (1.2) | 3.1 (1.3) | 2.5 (1.2) | 1.8 (1.1) |
| ≥3 poor prognostic factors*, n. (%) | 813 (69.0) | 1,210 (55.5) | 462 (50.4) | 1,256 (36.7) | 558 (29.6) |
| | Enrolment therapy: csDMARD | | | | |
| N | 720 | 1,110 | | 1,676 | 947 |
| Female gender, n. (%) | 582 (80.8) | 858 (77.3) | | 1,234 (73.6) | 695 (73.4) |
| Age in years | 56.4 (11.4) | 56.0 (11.5) | | 58.7 (12.8) | 58.6 (12.8) |
| Disease duration in years | 9.3 (8.6) | 8.3 (8.7) | | 6.3 (7.2) | 6.3 (7.5) |
| DAS28 | 5.4 (1.2) | 4.9 (1.3) | | 4.5 (1.3) | 4.5 (1.3) |
| Physical function (%)[#] | 64.0 (21.7) | 68.2 (21.3) | | 72.3 (21.5) | 69.8 (21.9) |
| No. previous csDMARDs | 2.0 (1.1) | 1.7 (0.9) | | 1.3 (0.7) | 0.8 (0.7) |
| ≥3 poor prognostic factors*, n. (%) | 340 (47.2) | 320 (28.8) | | 262 (15.6) | 134 (14.1) |

Values are presented as means (SD) unless otherwise specified.
bDMARD: biologic disease-modifying antirheumatic drug therapies; csDMARD: conventional synthetic disease-modifying antirheumatic drug therapies; DAS28: 28-joint-count disease activity score.
[#]Physical function is assessed by the Hannover Functional Status Questionnaire and which measures functional capacity as a percentage of full function.
*Poor prognostic factors are baseline variables defined as presence of rheumatoid factor and/or anticitrullinated protein antibodies, erythrocyte sedimentation rate > 50 mm/h, C-reactive protein > 30 mg/l, swollen joint count (based on 28 joints) > 17, DAS28 > 5.1, and presence of joint erosions.

the design and conduct of RABBIT is aligned to requirements of a disease register (30). On the other hand, the design of RABBIT also has some resemblance to RCTs: the enrollment at onset of a DMARD therapy guarantees that baseline data reflect the pre-treatment status of a patient and the standardised data collection ensures valid longitudinal observation of patients. The efforts taken to gain high-quality data in RABBIT, *i.e.* high response rates of physicians and patients (Fig. 2), minimal attrition (Fig. 4), and a standardised documentation of adverse events, are very high and come with price of high staff expenses.

Most of the characteristics and benefits of RABBIT are exclusive to studies with primary data collection and describe differences to administrative data. For instance, the monitoring of follow-up of patients is hardly possible with the use of secondary EHR or claims data with spontaneous reporting. This drawback impairs data quality and is likely to contribute to controversial results of studies using claims data. An example of such a controversy was the evaluation of the risk of serious infections after initiation of TNFi therapy. Two large scale observational studies with primary patient data, the British BSRBR and the Swedish ARTIS register, reported a higher risk of serious infections after initiation of TNFi (31, 32). In a study of Strangfeld *et al*. (33) in the RABBIT register these results were confirmed and it was additionally shown that patients that were lost to follow-up had highest incidence of serious infections. Contrary results were then found in a large-scale study using claims data bases of Grijalva *et al*. (34). In this study, no elevated risk of serious infections was found after initiation of TNFi. However, fewer than 30% of the patients were still observed after 12 months of follow-up. Given the extensive rate of dropouts these results are not interpretable; they also illustrate that the principle of *the more the merrier* does not apply to clinical data if the quality of the data is poor. Indeed, small to medium sized studies that comprise high quality data are to be preferred in terms of investigating the safety of drugs. This has been well demonstrated by several observational studies with long lasting patient follow-up (5, 35) and, since decades by the Rochester cohort (36). Weighing quality over quantity is for RABBIT also the primary guideline.

Another essential characteristic of studies using primary patient data is the availability of clinical data which provides important clinical insights that may not be discovered using administrative data. Regarding the risk of lower intestinal perforations (LIP) Xie *et al*. (2), reported an increased risk associated with tocilizumab, but was not able to describe the clinical presentation of patients with LIP. RABBIT found an increased risk of similar magnitude (21), but added relevant clinical information that many cases presented with atypically mild symptoms and that levels of CRP were not a reliable diagnostic marker for LIP, leading to potential delay in treatment.

A third example is the observation in RABBIT that patients who were under treatment with bDMARDs at the time point of a serious infection had a lower risk of developing septicemia and also a

lower mortality risk following infection (37). This result is of high clinical impact and would not be possible without detailed information on the exact dates of a) the occurrence of the serious infections in relation to b) the start and stop of treatments.

## Conclusion

We outlined the value of long-term observational studies with tightly monitored primary data collection, even with availability of ever increasing capacities to analyse large datasets from routine care. Clinical practice follows clinical need, and studies based upon secondary data have, among others, the problem that the level of information is influenced by the patient's decision to seek medical care – reflecting the severity of the disease. Secondary data comprise unique characteristics that definitely enable for investigation of research questions which have impact, *e.g.* on the quality of medical care. However, specific clinical questions require additional clinical information not routinely available. The examples that we have given – balancing risks and benefits of different treatments concerning serious infections, the likely benefit of biologic agents concerning the risk of septicemia after serious infection and the potentially altered clinical presentation of lower intestinal perforations in patients treated with IL-6 blockade – are of high clinical relevance. These results could be achieved only by careful, standardised primary data collection. Therefore, to ensure the safe use of an increasing variety of innovative medicines with different modes of action, standardised and complete clinical data are of utmost importance. This applies to the completeness of follow-up of individual patients to avoid selection bias during follow-up as well as the accuracy of the clinical data. With this, we are convinced that studies like RABBIT have lasting impact on daily clinical practice and lead to improve patient outcomes.

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