Chapter 2

Comparison of characteristics of (inter)national databases in rheumatoid arthritis: a systematic review

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ABSTRACT

Objective

To evaluate current (inter)national registers and observational cohorts in Europe, and to compare inclusion criteria, aims, collected data and participation in the EULAR repository.

Methods

We performed a systematic search strategy in six literature databases. Publications reporting European (inter)national prospective registers/cohorts including >200 RA patients with at least half a year of follow-up were selected.

Results

In total, 417 articles and abstracts were included, which described 4 international databases and 39 national databases/cohorts. International databases were of roughly similar design, frequency of data collection and selection criteria and are mostly initiated to monitor and compare clinical patient care among countries. National databases/cohorts vary in aims and inclusion criteria. Half of the national registers are connected to the EULAR repository of databases.

Conclusion

Our findings may indicate that among researchers there is little awareness of recommendations to set up registers or cohorts and of the existence of the database collaboration network of EULAR.

INTRODUCTION

The development of treatment care in rheumatoid arthritis (RA) is usually studied in randomized clinical trials (RCTs). However, it is well known that patients included in clinical trials often differ from patients in standard care due to specific inclusion criteria.[1,2] Patients in RCTs in general have higher disease activity and less or no co-morbidities compared to patients in cohorts.[3]

More valuable 'daily practice'-based information may be found in large representative long-term registries that have been established to monitor patients specifically in clinical practice.[4] Already some reviews compared characteristics of various registries to investigate differences between treatment results in clinical practice and RCTs.[5,6]

It appears that despite the availability of international recommendations on management of RA and similar access to the same drug therapies, important differences in outcomes remain. This may be due to variations in defining outcomes, or differences in local culture or variability in the use of biological agents (e.g. invoked by reimbursement policies or access to health care). In addition, the inclusion criteria, design and purpose of such registries may greatly influence the results of a database analysis. To improve collaboration between European rheumatologists, the European League Against Rheumatism (EULAR) has recently started a repository of databases, which can be used as a platform for researchers to start collaborative projects.

In this article we aim to give a complete overview of the existing large registers and cohorts in Europe (international, national, regional and local), to inform on participation of these databases in the EULAR repository and to provide details on inclusion criteria, aim of the registry and its data collection.

METHODS

Retrieval of possibly relevant references

A literature search was performed according to the PRISMA statement[7,8] for cohorts, registries and databases on of three types: international (more than one European country captured), national (captured centers in all parts of the country), regional (captured centers in more than one city in the same region) and local (captured one or more centers in a city). We searched in six databases; PubMed, Embassy, Web of Science (WOS), Academic Search Premier, Wiley-Blackwell and LWW. In collaboration with a trained librarian (JL), an

extensive search strategy was formulated (Attachment I). Search strategies for the other databases were formulated similarly but adjusted to the specific database. References were stored and deduplicated in a Reference Manager database. While recognizing the existence of numerous RA registries, we identified publications that were best served for our aims.

Selection of references

Criteria to include a reference or an article were:
1) The disease studied was at least RA
2) The database/study was prospective and longitudinal
3) The study was initiated in Europe
4) The study included more than 200 study participants
5) The study had at least half a year of follow-up.

Articles or abstracts were excluded if they described:
Cohorts/databases that also studied patients with non-rheumatologic diseases (such as studies based on hospital discharge registers, health service registers, and population based cohorts)
Case control studies.

The selection procedure consisted of 2 phases:
Two independent investigators (EG and RK) screened the references by title or abstract for selection. Differences were resolved by agreement. After this, the full text of the remaining articles and abstracts was read and reviewed extensively by one investigator (EG).
Additionally, a questionnaire was sent to 47 national societies of rheumatology connected to the EULAR asking for the presence and features of any RA or arthritis databases in their country. Both the questionnaire and the literature search were used to select the databases and cohorts for our study.

RESULTS

In total 5078 references were found with our systematic literature search (figure 1).

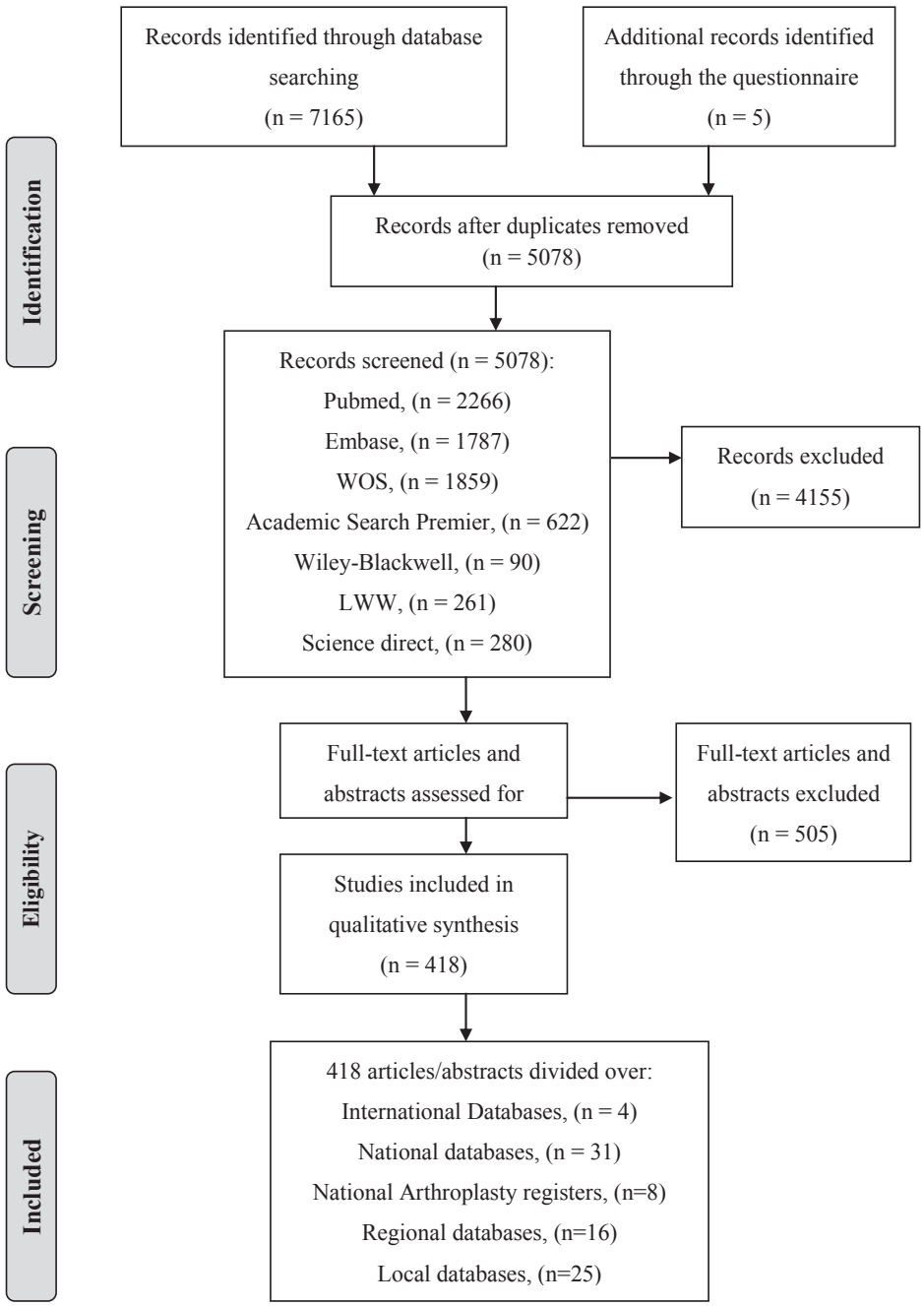

Figure 1. PRISMA Flow chart inclusion.

4155 references were excluded after screening of the titles and abstracts, which left us with 923 references. After reading the full text of the publications, another 506 references were excluded, resulting in a final set of 417 articles and abstracts for inclusion. The response rate of the questionnaire was 32/47 (68%) which provided us with 5 additional databases, of which no publications were found identified in the literature search. We identified combining both strategies 4 international databases, 39 national databases (7 of which were left out when they proved to be arthroplasty registers), 16 regional databases and 25 local databases. For some databases, more than one publication was available to describe all features. Approximately half of the databases were described once (n=33) or twice (n=12) but 5 databases were described in more than 20 publications (table 1).

The characteristics of the 4 international and the 32 national registers were further described and summarized in the tables, with focus on the following features: funding, aims, number of patients, year of inception, clinical evaluation of the physician, patient reported outcomes, laboratory information, radiographic imaging, drug treatment, frequency of data collection, selection criteria for enrolment into the registry, control groups, rheumatic diseases captured, connection to the EULAR repository of databases and the number of publications. Not all features we aimed to describe were reported in the publications, and we refer to them as 'not reported'.

International databases

Table 2 describes the four international databases that we have found: METEOR (Measurement of Efficacy of Treatment in the Era of Outcome in Rheumatology), GoTreatIt, Quest-RA (Quantitative Patient Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis) and Cererra (the European Collaborative Registries for the Evaluation of Rituximab in Rheumatoid Arthritis).[4,9,10]

All databases are practice-based registers, collecting clinical information on RA patients. The purpose of these databases is mostly to monitor clinical patient care and comparing patient care among countries. The available clinical collected outcomes are roughly similar in the four databases: DAS, HAQ and erosions.

METEOR and GoTreatIt are both internet-based instruments to monitor disease activity in RA and response to treatment.

Table 1. The number of publications per database.

Publications	**National/ international (n=43)**	**Regional (n=16)**	**Local (n=25)**	**Total (n=8)**
Databases not described in publications, n*	3	0	1	5
databases described in:				
1 publication, n	9	9	15	33
2 publications, n	8	1	3	12
3 publications, n	1	2	1	4
4 publications, n	3	1	1	5
5 publications, n	2	0	1	3
6 publications, n	3	0	0	3
7 publications, n	3	0	1	4
10 publications, n	1	0	0	1
11 publications, n	1	1	0	2
12 publications, n	1	0	0	1
13 publications, n	1	0	0	1
14 publications, n	1	0	0	1
16 publications, n	0	1	0	1
17 publications, n	0	0	1	1
18 publications, n	0	0	1	1
19 publications, n	0	1	0	1
≤20 publications, n	5	0	0	5

*5 databases were not described in the publications, they were found via the questionnaire, n=number.

They are based on and aim to promote using composite scores as tools to monitor disease activity.[10] Quest-RA is a monitoring program for standard care in RA.[4] Cererra is a drug-safety register with a fixed (every 0, 3, 6, 9 and 12 month's patients are seen) monitoring protocol the efficacy of rituximab in RA.[9] METEOR, QUEST-RA and GoTreatIt follow patients without fixed monitoring time points. The largest database is METEOR with more than 17.000 patients registered including at least one entry of disease activity; the database covering the highest number of countries (N=20) is QUEST-RA. METEOR, Quest-RA and Cererra are funded by pharmaceutical industry and GoTreatIt by the government.

Table 2. Characteristics of international databases/cohorts.

International database	*Funding*	*Aims*	*RA patients (n)*	*Year of inception*	*Physician/ clinical evaluation*	*Patient reported outcomes*	*Additional (labs/ radiographies/ imaging)*	*Drug treatment recorded*	*Articles/ abstracts published (n)*
METEOR (Measurement of Efficacy of Treatment in the 'Era of outcome' in Rheumatology)[1]	3	3	Ongoing, 17.700	2008	DAS, SJC, TJC, VAS (global), SDAI, CDAI	HAQ, VAS pain/global	Erosions, RF, CCP, ESR, CRP	b and csDMARDs, NSAIDs, glucocorticoids	1
Quest-RA (Quantitative Patient Questionnaire Monitoring in Standard Clinical Care of Patients with Rheumatoid Arthritis)[4]	3	3	Ongoing, 7.568	2005	DAS, SJC, TJC, VAS (global)	HAQ, RADAI, ROAD, VAS pain/global	Erosions, RF, ESR, CRP	b and csDMARDs, NSAIDs, glucocorticoids	6
Cererra (European Collaborative Registries for the Evaluation of Rituximab in Rheumatoid Arthritis)[9]	3	1	Ongoing/ Closed, is not reported 2.019	Not reported	DAS, SJC, TJC, VAS (global)	HAQ, VAS pain/global	Erosions, RF, CCP, ESR, CRP	b and csDMARDs, glucocorticoids	4
GoTreatIt	1	3	Ongoing, ~8.000	2004	DAS, SJC, TJC, VAS (global)	HAQ, VAS pain/global	Erosions, RF/CCP factor, ESR/CRP	b and csDMARDs, NSAIDs, glucocorticoids	0

Table 2 (continued). Characteristics of international databases/cohorts.

International database	*Frequency of Data collection (mo)*	*Selection criteria for enrolment*	*Control group*	*Rheumatologic Diseases captured*	*European countries captured (n)*	*Connected to the EULAR*
METEOR (Measurement of Efficacy of Treatment in the 'Era of outcome' in Rheumatology)[10]	Continuous	RA patients Spa at all stages	No	Early and established RA	16	No
Quest-RA (Quantitative Patient Questionnaire Monitoring in Standard Clinical Care of Patients with Rheumatoid Arthritis)[4]	Continuous	RA patients, usual patient care	No	Early and established RA	20	No
Cererra (European Collaborative Registries for the Evaluation of Rituximab in Rheumatoid Arthritis)[9]	Fixed protocol, Every 0,3,6,9,12	RA patients treated with rituximab	No	Early and established RA	10	No
GoTreatIt	Continuous	All patients with rheumatic diseases	No	All rheumatic diseases	2	No

Funding: 1) government 3) Pharmaceutical industry, Aims: 1) efficacy and safety of biological or other treatments 3) monitoring/ benchmarking (disease activity) for clinical practice, DAS=Disease Activity Score, HAQ=Health Assessment Questionnaire, SJC=swollen joint count, TJC=tender joint count, VAS=visual analogue scale, ESR=erythrocyte sedimentation rate, CCP=anti-cyclic citrullinated peptide, CRP=C-recreative proteïne, RF=rheumatoid factor, DMARDs=disease-modifying anti rheumatic drugs (b=biological, cs=conventional), n=number, mo=months, NSAIDs=nonsteroidal anti-inflammatory drugs, RA=rheumatoid arthritis.

National databases/cohorts

Distribution: Attachment II; table 1 shows the national databases and cohorts in Europe. 16 European countries have nationally based databases or cohorts. Most of them were found in France (n=4), Spain (n=4) and the United Kingdom (n=4). However, the largest registers were found in the United Kingdom, Germany and Denmark.

Size/number of publications: The largest registers with more than 10.000 patients are the British Society for Rheumatology Rheumatoid Arthritis Register (BSRBR) (N≈20.000, 44 publications), the German Collaborative Arthritis Centers (N≈15-17,000, 26 publications), the Danish Registry for Biologic Therapies in Rheumatology (DANBIO) (N≈10.000, 14 publications) and the German biologics register (RABBIT) (N≈12.303, 20 publications). DANBIO, BSRBR and Rabbit are aiming at efficacy of the biologic drugs and all include early and established RA patients, while the German Collaborative Arthritis Centers is established for epidemiologic purposes and includes all RA patients, without restriction of drug use.[11-14] Eleven databases are currently closed, 15 are ongoing and for six databases the size was not reported (Attachment II; table 1).

Year of inception: The inception of the cohorts and registers varies between 1986 and 2011. The largest registers were not all the oldest registers. The oldest cohort is the Early Rheumatoid Arthritis study (ERAS) which started in the United Kingdom, in 1986. Also long running are the Norfolk Arthritis Register (NOAR, 1989), the national database of the German Collaborative Arthritis Centers (since 1993), the Early Swedish Rheumatoid Arthritis Register (RAMONA) (since 1995) and the Swiss Clinical Quality Management program for RA (SCQM-RA) (since 1997). These older databases differed in aims and inclusion criteria. ERAS and RAMONA primarily aimed at monitoring clinical disease activity and included only early RA patients.[15,16] NOAR, SCQM-RA and the German Collaborative Arthritis Center have different purposes (predictive, monitoring and epidemiologic respectively) but similar inclusion criteria.[13,17,18]

Diseases captured: 23 databases described both early and established RA, 6 only early RA and 2 only established RA. Approximately half of the databases are covering more rheumatologic diseases besides RA such as Spondyloarthritis or Psoriatic Arthritis (Attachment II; table 1).

Selection criteria for enrolment into the registry: selection criteria vary with the main aims of the registry. We divided the registries in two sections based on aims as described in the publications: Fifteen registries have as primary aim to investigate efficacy and safety of biologic (or other) treatments. Inclusion criteria for these registers were for 14/15 both early and established RA. Most (11/15) of the efficacy registers were biologic registers. 8 of the registers aim at monitoring disease activity and benchmarking for clinical practice purposes. Inclusion criteria were for 4/6 both early an established RA patients, for 1 register established and for 3 registers early RA patients. Half of the latter register types are not connected to the EULAR repository of databases. Four registries serve epidemiological purposes, studying the prediction of outcome and aetiology. Inclusion criteria varied from established RA (n=1) to both established and early RA (n=3). Four registers aimed at monitoring one (biologic) drug in particular (Autoimmunity and Rituximab in RA cohort, MAbThera registry in RA, Orencia and RA study, medico-economic evaluation of infliximab study.[19-21]

Therapies: DMARDs and/or biologic agents are registered in 31/32 databases.

Frequency of data collection: In 11 of the databases, data collection is performed on a continuous basis, each time the patient visits the physician and not only at predefined time points. For the fixed protocols, seven databases include data collected every 3 months and 7 databases collected data every 6 months (Attachment II; table 1).

Physician/clinical evaluation: 31 registries collect Disease Activity Score (DAS) and/or DAS components, 19 of the registers use the DAS28 score. 4 registers report CDAI and SDAI and four registries also report morning stiffness.[11,14,16,19, 22-24]

Patient reported outcomes (PROs): 25 registries report results of the Health Assessment Questionnaire (HAQ), or alternatives/derivatives of the HAQ such as the Functional Status Questionnaire Hannover (FFbH). Results of the short-form-36 health survey questionnaires (SF-36) was reported in the BSRBR, the Early Rheumatoid Arthritis Network cohort (ERAN), the Gruppo Italiano Artrite Reumatoide Aggressiva (GIARA)-registry, the Norwegian disease-modifying antirheumatic drug register (NOR-DMARD) registry, study for the medico-economic evaluation of infliximab (EMER study), NOAR and the rheumatic diseases Portuguese register (Reumapt).[12,17,20,25-28] The RADAI (self-administered

rheumatoid arthritis disease activity index) was reported in the Swiss SCQM-RA and in the Belgian MIRA register.[18,21]

Additional (Labs/radiographies/imaging): All registries report CRP or ESR as acute phase reactants; radiographic information was collected in 50% of the registers, however for biological databases radiological measures (such as x-rays) were not always done or reported (Attachment II; table 1).

Funding: 16 of the databases are funded by pharmaceutical industries; also government, charity, health care, private sources and rheumatologic associations are funding registers. Most (11/14) of the biologic registers were funded by pharmaceutical companies (Attachment II: table 1).

Connection to EULAR: 16 of the 32 databases were connected to the EULAR repository of databases.[11-15,17-19,22,27-33]

Main differences: databases were distributed over 16 national countries, which shows that the population is various. The smallest database was Iceland's biologics register containing 214 subjects and the largest was BSRBR, with approximately 20.000 subjects.[12] A wide range between years of inception (24 years between the youngest (Biologic register Austria) and the oldest (ERAS) cohort) shows that there is a continuous need, and apparently renewal of funds, to start these registries and databases. Furthermore there are differences in inclusion criteria (only RA or also other diseases, only early RA, or also established RA, only one biologic therapy or all treatments), and in timing and regulation of data collection.

Main similarities: almost all databases collected similar drug information and clinical outcomes (patient reported outcomes and physicians evaluation).

DISCUSSION

In this systematic review we described four international and 32 national RA databases and cohorts of rheumatoid arthritis patients. The international initiatives have roughly similar aims, unrestricted inclusion criteria and continuous data collection, enabling comparisons of patients in daily practice between countries. The included patients have various degrees of disease severity, and are treated with a wide range of synthetic and biologic DMARDs.[4,9,10] It is not clear which percentages of eligible patients are included, and by what selection criteria this is determined. Thus, the included patients appear to represent patients from

normal daily practice, but may still present a selected population. Having been initiated relatively recently (between 2004 and 2008), these databases are mostly still collecting data and have not led to many publications, in comparison to some of the national databases .All four international initiatives are funded by pharmaceutical industry or the government and they are not connected to the EULAR repository of databases.

The national RA databases were set up between 1986 and 2010; approximately half of them are still ongoing.[11-40] 16 of these national databases were mentioned in the EULAR repository for databases. Although there are differences in inclusion criteria, aim, frequency of data collection and distribution among countries in Europe, the national databases generally collect similar patient reported outcomes, physician clinical evaluation and medication. This may stem from government requirements to monitor safety of recently introduced therapies, which may also explain involvement of sponsors from the pharmaceutical industry. Four databases appear to have been initiated to monitor patients treated with one (biologic) drug in particular.[19-21] The similarities also may indicate that there is not so much a need for new data, but a desire to 'own' one's own data to do research and write scientific papers. However, research on individual databases may be hampered by small numbers, but the (small) differences among the registries make the data of various databases difficult to compare or pool with others. This itself may be a reason to start yet again a new (large and/or international) database or registry. Curtis et al. and Zink et al. focused on biological registers while comparing characteristics of international databases. They found in concordance to our results that there is heterogeneity among databases, which Zink et al. suggest may lead to further analyses and new information.[5, 6]

Mostly the oldest and largest national databases are connected to the EULAR repository of databases.[11-18] It appears not all researchers are aware of or follow recommendations to set up registries or cohorts, nor aware of the EULAR network and database repository that aims to support collaboration between database researchers. Since databases and registries mostly have been initiated to provide information that may be missed in RCTs, it is relevant to identify if the results of these initiatives have been published in medical journals. Without publication, the effort of building the database may not be matched by the output of little information to few direct users. We found that in particular results from older and larger databases have been published. Some registers had few or no publications, which might be

due to difficulties in retrieving information from the registry, possibly due to the size and set up of the registry, incomplete data collection or poor IT support. These problems could be prevented when researchers connect their registers to the EULAR repository of databases. It has to be kept in mind that despite resembling daily practice, intentional or unintentional selection of patients whose data will enter the database may compromise generalizability of the database results.

In conclusion, through a systematic literature search and an additional inventory by questionnaire we found four international RA databases with similar inclusion criteria and content and frequency of data collection, and 32 national RA databases or registries, which differ substantially. Half of these databases, the oldest and largest with most publications, are connected to the EULAR repository of databases. It may be worthwhile for the others to join initiatives such as the EULAR repository for databases for collaboration between cohorts, to decrease differences in database structure and content and to improve quality of research and output. Since half of the databases is not joining the EULAR repository of databases, our results provide a more complete overview of the current present databases than the EULAR repository of databases. This overview is useful for researchers that want to start collaborations with researchers of databases that answer their research questions. Also researchers of existing databases can collaborate and compare data. Via this overview they can easily find the aims, inclusion and data collection of existing databases.

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Attachment I. Full search strategy for PubMed.

("Arthritis, Rheumatoid"[mesh] OR "Rheumatoid Arthritis"[all fields] OR ra[ti] OR "Rheumatoid Nodule"[all fields] OR "Rheumatoid Vasculitis"[all fields]) AND ("Databases, Factual"[Mesh] OR "database"[all fields] OR "databases"[all fields] OR "Registries"[Mesh] OR "registry"[all fields] OR "registries"[all fields] OR "register"[all fields] OR "internet"[Mesh] OR "internet"[all fields] OR "software"[mesh] OR "software"[all fields] OR "Cohort Studies"[Mesh] OR "cohort"[tiab]) AND (“international”[tiab] OR “national”[tiab] OR "Europe"[Mesh] OR "europe"[tiab] OR "european"[tiab] OR "Andorra"[tiab] OR "Andorran"[tiab] OR "Austria"[tiab] OR "Austrian"[tiab] OR "Belgium"[tiab] OR "Belgian"[tiab] OR "Albania"[tiab] OR "Albanian"[tiab] OR "Estonia"[tiab] OR "Estonian"[tiab] OR "Latvia"[tiab] OR "Latvian"[tiab] OR "Lithuania"[tiab] OR "Lithuanian"[tiab] OR "Baltic"[tiab] OR "Bosnia-Herzegovina"[tiab] OR "Bosnian"[tiab] OR "herzegovinian"[tiab] OR "Bulgaria"[tiab] OR "Bulgarian"[tiab] OR "Croatia"[tiab] OR "Croatian"[tiab] OR "Czech"[tiab] OR "Hungary"[tiab] OR "Hungarian"[tiab] OR "Macedonia"[tiab] OR "Macedonian"[tiab] OR "Moldova"[tiab] OR "Moldovian"[tiab] OR "Montenegro"[tiab] OR "Montenegran"[tiab] OR "Poland"[tiab] OR "Polish"[tiab] OR "Republic of Belarus"[tiab] OR "belarian"[tiab] OR "Romania"[tiab] OR "Romanian"[tiab] OR "Russia"[tiab] OR "Russian"[tiab] OR "Serbia"[tiab] OR "Serbian"[tiab] OR "Slovakia"[tiab] OR "Slovakian"[tiab] OR "Slovenia"[tiab] OR "Slovenian"[tiab] OR "Ukraine"[tiab] OR "Ukrainian"[tiab] OR "Yugoslavia"[tiab] OR "Yugoslavian"[tiab] OR "Finland"[tiab] OR "Finnish"[tiab] OR "France"[tiab] OR "French"[tiab] OR "Germany"[tiab] OR "German"[tiab] OR "Gibraltar"[tiab] OR "Gibraltarian"[tiab] OR "Great Britain"[tiab] OR "British"[tiab] OR "United Kingdom"[tiab] OR "Greece"[tiab] OR "Greek"[tiab] OR "Iceland"[tiab] OR "Icelandic"[tiab] OR "Ireland"[tiab] OR "Irish"[tiab] OR "Italy"[tiab] OR "Italian"[tiab] OR "Liechtenstein"[tiab] OR "Luxembourg"[tiab] OR "Luxembourgian"[tiab] OR "Monaco"[tiab] OR "Monegasque"[tiab] OR "Netherlands"[tiab] OR "dutch"[tiab] OR "Portugal"[tiab] OR "Portuguese"[tiab]

Attachment II: Table 1. Characteristics national databases/cohorts.

National databases by country	Funding	Aims Primary	Aims Secondary	Size, RA patients (N)	Year of inception	Physician/clinical evaluation	Patient reported outcomes	Articles/ abstracts published (N)	Connected to the EULAR
Germany									
Rabbit (German Biologics Register)[14]	3	1		Ongoing, 12.303	2001	DAS28, SJC28, TJC28, morning stiffness	FFbH, VAS (general health, pain, fatigue)	20	Yes
National database of the German Collaborative Arthritis Centers[13]	1	2	9, 3, 10	Ongoing 5-17.000 py	1993	Severity of disease, VAS (global), DAS28, SJC28, TJC28	FFbH, VAS (pain, global)	26	Yes
United Kingdom									
BSRBR (British Society for Rheumatology RA Register)[12]	3	1	9, 7	Ongoing ~ 20.000	2001	DAS28, SJC28, TJC28, clinical questionnaire	HAQ, SF-36, patient questionnaire	44	Yes
ERAN (Early RA Network cohort)[27]	5	3	10, 1	Ongoing, 1.180	2002	DAS28, SJC28, TJC28, VAS (global), morning stiffness	HAQ, SF-36, VAS (global)	5	Yes
ERAS (Early RA Study)[33]	2	3	2, 4, 9, 7	Ongoing, 1.460	1986	SJC, TJC, RAI	HAQ, VAS (pain, global)	12	Yes
Norfolk ArthritisRegister(NOAR)[17]	2	4	2, 6	ongoing, 1.745	1989	SJC, TJC, DAS, DAS28, TJC28, SJC28	HAQ, SF-36	32	Yes
Scotland									
Sera (Studies of the Etiology of RA)	4	7		Ongoing, 1.800	2010/ 2011	DAS, SJC, TJC, VAS (global)	HAQ, VAS (pain, global)	0	No

National databases by country	Additional (labs/ radiographies/ imaging)	Drug treatment recorded	Frequency of data collection (mo)	Selection criteria for enrollment into registry	Control group	Rheumatic diseases captured
Germany						
Rabbit (German Biologics Register)[14]	ESR, CRP, RF	cs or bDMARDs NSAIDs, glucocorticoids	Every 0, 3, 6, 12, until 120	RA, start bDMARDs	conventional DMARD	Early and established RA, AS, PsA
National database of the German Collaborative Arthritis Centers[13]	ESR/CRP, RF	cs or bDMARDs Glucocorticoids	continuous	inflammatory rheumatic disease in daily practice	General population/ patients of same Rheumatology unit	Early/ established RA, other rheumatologic diseases
United Kingdom						
BSRBR (British Society for Rheumatology RA Register)[12]	ESR/CRP	cs or bDMARDs NSAIDs	Every 0, 6, 12, 18, 24, 30, 36, then annually	RA starting b or csDMARD.	Active RA patients treated with csDMARDs.	Early/ established RA and other rheumatologic diseases
ERAN (Early RA Network cohort)[27]	RF, erosions, X-rays, ESR/CRP	DMARDs	Every 0,3, 6, then annually	Newly diagnosed RA patients in routine care	General population/ patients of same Rheumatology unit	Early RA
ERAS (Early RA Study) [33]	ESR, RF erosions	Second line drugs or DMARDs	Annually	RA symptom > 2yr, no use of second line drugs	Patients not fulfilling 1987 revised ACR criteria for RA	Early RA
Norfolk Arthritis Register (NOAR)[17]	X-rays, Larsen, CRP, RF, CCP	-	Annually	Patient ≥16 years, ≥2 inflamed joints ≥4weeks.	Not reported	Early/ established RA
Scotland						
Sera (Studies of the Etiology of RA)	ESR/CRP, laboratory serum	Not reported	Not reported	Newly diagnosed RA/UA	Not reported	Early RA/UA

National databases by country	Funding	Aims Primary	Aims Secondary	Size, RA patients (N)	Year of inception	Physician/ clinical evaluation	Patient reported outcomes	Connected to the EULAR	Articles/ abstracts published (N)
Portugal									
Reumapt. (Rheumatic Diseases Portuguese Register)[25]	3	3		Ongoing, ~2.500	2008	DAS28, SJC28, TJC28, VAS (global)	VAS (pain, global), SF-36, HAQ	No	1
Finland									
rob-fin (National Register of Biological Treatment in Finland)[32]	3	1	9	Ongoing, <1.688	1999	TJC, SCJ, VAS (global)	HAQ, VAS (general, pain, global)	Yes	7
Sweden									
ARTIS (Swedish Biologics Register)[31]	3	1		Closed, 7.354	1998	DAS28, SJC28, TJC28, VAS	VAS (global, pain), HAQ	Yes	11
RAMONA (Swedish early RA register)[15]	1	3	2, 7	Closed, 6.745	1995	DAS28, SJC28, TJC28	HAQ	Yes	7
Swiss									
SCQM-RA (Swiss Clinical Quality Management program for RA)[18]	6	3	1, 7	Ongoing, 6.300	1997	DAS28, SJC28, TJC28	HAQ, RADAI	Yes	11

National databases by country	Additional (labs/ radiographies/ imaging)	Drug treatment recorded	Frequency of data collection (mo)	Selection criteria for enrollment into registry	Control group	Rheumatic diseases captured
Scotland						
Sera (Studies of the Etiology of RA)	ESR/CRP, laboratory serum	Not reported	Not reported	Newly diagnosed RA/UA	Not reported	Early RA/UA
Portugal						
Reumapt. (Rheumatic Diseases Portuguese Register)[25]	ESR/CRP, X-ray, SHS,CCP	cs or bDMARDs	Continuous	rheumatic patients receiving cs or bDMARDs	Not reported	Early RA/ established RA, AS, SPA and JIA
Finland						
rob-fin (National Register of Biological Treatment in Finland)[32]	ESR/CRP	cs or bDMARDs glucocorticoids,	Every 6	Active RA, DMARDs response not satisfied, start TNF blocker	RA patient using DMARD	Early/ established RA
Sweden						
ARTIS (Swedish Biologics Register)[31]	ESR/CRP	cs or bDMARDs NSAIDs, corticoids	Every 0, 3, 6, 12, 18, 24 after start bDMARD	RA patients starting biologics	Patients with RA/ comorbidity	Early/ established RA
RAMONA (Swedish early RA register)[15]	RF, ESR/CRP	DMARDs	Every 0, 3, 6, 12, 18 , 24 after start bDMARD	Diagnosis of RA < 12 mo after symptom onset	Patients with RA/ comorbidity	Early RA
Swiss						
SCQM-RA (Swiss Clinical Quality Management program for RA)[18]	ESR/CRP, radiograpy	cs or b DMARDs glucocorticoids	Continuous	patients receiving cs or bDMARDs	Patients receiving other drugs	Early/ established RA, AS, PsA

National databases by country	Funding	Aims Primary	Aims Secondary	Size, RA patients (N)	Year of inception	Physician/ clinical evaluation	Patient reported outcomes	Connected to the EULAR	Articles/abstracts published (N)
France									
ORA (Orencia and RA) [37]	3	1		Closed, 1.000	2008	DAS28,SJC28, TJC28	Not reported	No	1
ESPOIR (French Early Arthritis Cohort) [19]	5	4	5, 7, 9	Closed, 813	2002	TJC28, SJC28, DAS28, morning stiffness	HAQ	Yes	21
EMER study (medico-economic evaluation of infliximab)[20]	5	9		Not reported, 635	2001	VAS (global), DAS28, SJC28, TJC28	VAS (pain, global), HAQ, SF-36	No	1
AIR RA (autoimmunity and Rituximab in RA)[37]	3	4	2	Closed, 2.000	2005	DAS28, SJC28, TJC28	Not reported	No	2
Spain									
BIOBADASER (Spanish Registry of biological therapies in rheumatic diseases)[30]	5	1	2, 10	Closed, ~ 6.000	2000	Not reported	Not reported	Yes	10
EMECAR (Spanish RA Registry Cohort Study)[29]	5	8	2, 4	Closed, 789	1999	DAS28, SJC28, TJC28	MHAQ	Yes	6
SERAP (Evaluation of a Model for Arthritis Care in Spain)[22]	3	1	2, 5	Closed, 777	2004	DAS28, SJC28, TJC28, morning stiffness	HAQ	Yes	2

National databases by country	Additional (labs/ radiographies/ Imaging)	Drug treatment recorded	Frequency of data collection (mo)	Selection criteria for enrollment into registry	Control group	Rheumatic diseases captured
France						
ORA (Orencia and RA)[37]	ESR/CRP	cs or bDMARDs,	Every 0, 3, 6, then every 6	RA patients	Not reported	Early/ established RA
ESPOIR (French Early Arthritis Cohort)[19]	RF, erosions, CRP, CCP, immunologic/ biologic data	DMARDs	Every 0,6 and 12 for 10 years	Age 18-70, <2 TJC/SJC, 6 weeks to 6 mo RA or suspected RA, DMARD naïve	Not reported	Early RA
EMER study (medico-economic evaluation of infliximab)[20]	ESR/CRP	bDMARDs	2 years, Continuous	RA patients	Not reported	Early/established RA
AIR RA (autoimmunity and Rituximab in RA)[37]	RF, ESR/CRP	bDMARDs	<2 years, 7 treatments	RA patients	Not reported	Early/ established RA, SLE
Spain						
BIOBADASER (Spanish Registry of biological therapies in rheumatic diseases)[30]	ESR/CRP	cs or bDMARDs, NSAID	continuous	bDMARD users	EMECAR cohort	Early/ established RA and other rheumatic diseases
EMECAR (Spanish RA Registry Cohort Study)[29]	ESR/CRP, RF erosions, radiology	bDMARD, NSAID, glucocorticoids	continuous	RA patients	BIOBADASER cohort	Early RA
SERAP (Evaluation of a Model for Arthritis Care in Spain)[22]	CRP, ESR, RF factor	Not reported	Every 6	Suspected RA (<1 SJC; pain, morning stiffness <30 minutes), >16 years, first joint manifestation <6 months before study	Non RA patients	Early RA

National Databases by country	Funding	Aims Primary	Aims Secondary	Size, RA patients (N)	Year of inception	Physician/ clinical evaluation	Patient reported outcomes	Connected to the EULAR	Articles/ abstracts published (N)
Study of Ultrasound Group of the Spanish Society of Rheumatology [38]	3	3		Not reported, 367	2004	SJC28, TJC28, DAS28	HAQ, VAS (pain)	No	1
Denmark									
DANBIO (Danish Registry for Biologic Therapies in Rheumatology)[11]	3	1	4, 3	Closed, ~10.000	2000	DAS28, SJC28, TJC28, CDAI	HAQ, HR-QoL, VAS (pain, fatigue, global)	Yes	14
Norway									
Nor-DMARD (Norwegian register of DMARD prescriptions for patients with inflammatory arthropathies)[35]	5	1	3, 7	Closed, ~3.000	2000	DA2S28, SJC28, TJC28	VAS (pain, global, fatigue), HAQ, SF-36	No	4
Biorheuma (Biologic treatment of patients suffering from inflammatory Rheumatic disorders in Norway)	1	1		Closed, ~12.000	Not reported	DAS, SJC, TJC	VAS (pain, global)	No	0
Belgium/Luxembourg									
Mira registry Belgium/Luxembourg (MabThera In RA)[21]	3	1		Ongoing, approx. 40% of centers in Lux/Belg	2006	DAS28, SJC28, TJC28	VAS (global) HAQ, RADAI	No	2

National Databases by country	Additional (labs/radiographies/ Imaging	Drug treatment recorded	Frequency of data collection (mo)	Selection criteria for enrollment into registry	Control group	Rheumatic diseases captured
Study of Ultrasound Group of the Spanish Society of Rheumatology[38]	RF, ESR, CRP	cs or bDMARDs	Every 0, 3, 6 and 12	RA according to the 1987 criteria	Not reported	Early/ established RA
Denmark						
DANBIO (Danish Registry for Biologic Therapies in Rheumatology)[11]	Erosions, CRP, x-ray, sharp score	cs or bDMARDs	Continuous	rheumatic patients using bDMARDs	Rheumatic patients from the same department of rheumatology	Early/ established RA, AS, PsA
Norway						
Nor-DMARD (Norwegian register of DMARD prescriptions for patients with inflammatory arthropathies)[35]	CRP, ESR, IgM RF factor, erosions	cs or bDMARDs NSAIDs, glucocorticoids	Every 0, 3, 6, 12, then annually	All consecutive DMARD prescriptions in adult patients (³ 18 years) with inflammatory arthropathies	Not reported	Early/ established RA and other inflammatory arthropaties
Biorheuma (Biologic treatment of patients suffering from inflammatory Rheumatic disorders in Norway)	CRP/ESR	bDMARDs	Not reported	bDMARD users	Not reported	Early/ established RA and other inflammatory rheumatic disorders
Belgium/Luxembourg						
Mira registry Belgium/Luxembourg (MabThera In RA)21	ESR, RF, CCP	bDMARDs	Every 8 weeks	RA patients	Not reported	Early/ established RA

National Databases by country	Funding	Aims Primary	Aims Secondary	Size, RA patients (N)	Year of inception	Physician/ clinical evaluation	Patient reported outcomes	Connected to the EULAR	Articles/ abstracts published (N)
Belgium EAP (Belgian Expanded Access Program RA Study)[40]	3	3	1	Not reported, 511	2000	VAS (global), DAS28, SJC28, TJC28	HAQ, VAS (global)	No	1
Greece									
Hellenic biologic register[39]	3	1	3	Ongoing, ~ 1.100	2003	DAS, TJC, SJC	HAQ	No	3
Czech Republic									
Attra (Czech National Registry of biological treatments)[23]	1	1		Not reported, 1.700	2002	DAS, TJC, SJC, CDAI, VAS (global)	VAS (global)	No	7
Iceland									
Icebio (Iceland's biologics register)[34]	3	1	7	Ongoing, 214	Not reported	DAS, VAS (global), SJC, TJC	HAQ, VAS (global, pain)	No	2
Austria									
CARAbase (care for RA database)[24]	Not reported	3		Not reported	2002	DAS, CDAI, SDAI, TJC, SJC, VAS (global)	VAS (global)	No	0
Bio-reg (biologic register)	3	1	9	Not reported	2010	DAS, TJC, SJC, CDAI, VAS (global)	VAS (global) HAQ	No	0

National Databases by country	Additional (labs/ radiographies /imaging	Drug treatment recorded	Frequency of data collection (mo)	Selection criteria for enrollment into registry	Control group	Rheumatic diseases captured
Belgium EAP (Belgian Expanded Access Program RA Study)[40]	CRP, ESR, RF	cs or bDMARDs	Every 0, 2,6 weeks, then every 8 weeks	RA patients	Not reported	Established RA
Greece						
Hellenic biologic register[39]	ESR/CRP	bDMARDs	Continuous	RA, Spa patients	Not reported	Early/established RA, SPA
Czech Republic						
Attra (Czech National Registry of biological treatments)[23]	X-rays, CRP	cs or bDMARDs,	Continuous	Failure of 1 DMARD, DAS 28 > 5.1, no contraindication TNF	Not reported	Early/established RA, AS, PSA, JIA
Iceland						
Icebio (Iceland's biologics register)[34]	ESR/CRP, RF	bDMARDs	Continuous	Rheumatic diseases	Not reported	Early/established RA, PsA, SPA, SLE
Austria						
CARAbase (care for RA database)[24]	ESR,CRP	Cs or bDMARD	Continuous	RA	Not reported	Early/ established RA
Bio-reg (biologic register)	Radiologic progression, RF factor, CCP, CRP	bDMARDs	Every 6	Patients with inflammatory diseases	Not reported	Early/ established RA and other Inflammatory diseases

National Databases by country	Funding	Aims Primary	Aims Secondary	Size, RA patients (N)	Year of inception	Physician/clinical evaluation	Patient reported outcomes	Connected to the EULAR	Articles/ abstracts published (N)
Italy									
GISEA (Italian Group for the Study of Early Arthritis)[36]	4	1	2, 3	Ongoing, ~ 1.000	2003	DAS, SJC, TJC, (VAS global)	VAS (global)	No	1
GIARA (Italian registry of aggressive RA)[28]	3	2	3	Ongoing, 1.218	2001	DAS, SJC, TJC, VAS (global)	HAQ, VAS (global), SF-36	Yes	2

National Databases by country	Additional (labs/ radiographies/ imaging	Drug treatment recorded	Frequency of data collection (mo)	Selection criteria for enrollment into registry	Control group	Rheumatic diseases captured
Italy						
GISEA (Italian Group for the Study of Early Arthritis)[36]	ESR/CRP	bDMARDs	Every 6	Patients aged above 18	Not reported	Early/ established RA and other rheumatologic diseases
GIARA (Italian registry of aggressive RA)[28]	RF, CRP/ESR, erosions	DMARDs, NSAIDs, glucocorticoids,	Every 6	RA<5 years classified as having established RA	Not reported	Established RA

Funding: 1) government; 2) charity; 3) pharmaceutical industry; 4) other private sources; 5) Mixed, Aims 1) efficacy and safety of biological (or other) treatments; 2) determining epidemiological core data (Incidence or prevalence); 3) monitoring/benchmarking (disease activity) for clinical practice; 4) research aiming at outcome and prediction of outcome; 5) Registration of diagnoses, 6) registries aiming at natural course of the disease; 7) Research aiming to investigate causal mechanisms; 8) Study comorbidities; 9 Medio economic evaluation 10) Educational studies (e.g. implementation or recommendations), DAS=Disease Activity Score, HAQ=Health Assessment Questionnaire, SJC=swollen joint count, TJC=tender joint count, VAS=visual analogue scale, ESR=erythrocyte sedimentation rate, CRP=C-reactive protein, RF=Rheumatoid Factor, CCP=anti-cyclic citrullinated peptide, DMARDs=disease-modifying anti rheumatic drugs (b=biologic, cs=conventional), NSAIDs=nonsteroidal anti-inflammatory drugs, RA=rheumatoid arthritis, CDAI= Clinical Disease Activity Index, SDAI= Simplified Disease Activity Index.