Review

Importance of registries in informing clinical practice for arthritis

Lewis Carpenter[1], Elena Nikiphorou[2] & Adam Young*[1,3]

Practice Points

- Cohort studies and registries provide information on clinical guidelines and quality of care, drug safety and benefit–risk data, and health-related outcomes, including quality of life and clinical effectiveness.
- The prevalence of rheumatoid arthritis (RA) from registries in the UK in the 1990s was 1.16% in women and 0.44% in men, which had decreased in women and increased in men from the 1950s.
- RA has a very variable course, but is generally set in the first few years.
- Reduced functional ability is frequently an early feature.
- Rheumatoid factor remains the most useful prognostic factor.
- The long-term adverse effects of biologics include a slight increase in opportunistic infections.
- The identification of 'early RA' is critical and drives forward improvements in management.
- The continuous use of contemporary data is important for national policy making organizations (the National Audit Office and NICE).
- Current databases underpin future and more ambitious national initiatives.

SUMMARY: The gold standard in research for evidence that underlies clinical practice is the randomized controlled trial. In recent years it has been accepted that observational studies, which include disease and drug registries and cohort studies, are very important sources of data not available from randomized clinical trials, and the two different approaches complement one another. In rheumatology, the development of clinical guidelines, standards of care and health policies, and appraisal of new drugs by NICE, all rely on clinical outcomes, prognostic factors and responses to drug therapies provided by both sources. Observational

[1]The Center for Lifespan & Chronic Illness Research, University of Hertfordshire, Hatfield, UK
[2]Department of Rheumatology, Addenbrookes Hospital, Cambridge, UK
[3]Department of Rheumatology, City Hospital, St Albans, AL3 5PN, UK
*Author for correspondence: adam.young@nhs.net

Future Medicine part of fsg

studies and registries in arthritis have promoted greater collaborations between academics and clinicians, and with patient support groups and public health. The main strengths of observational studies are that, first, they reflect 'real-world' practice and, second, they can achieve prolonged follow-up. As the management of chronic conditions such as arthritis becomes more complex and health economic issues more important in the 21st century, it is probable that more reliance will be placed on these types of studies.

Disease or patient registries are collections of secondary data related to patients with a specific condition or intervention. In previous decades, a disease registry in its simplest form would consist of a diagnostic index of patients collected at one point in time on paper cards kept by an individual physician. Now registries vary in sophistication from simple computer spreadsheets, with confined access, to very complex databases, available online across multiple institutions. Although they may just provide a snapshot of a condition or drug, many have extended to include regular yearly follow-ups and collection of outcomes, either directly or through database linkage via unique personal identification codes, resulting in similar aims and designs to observational and longitudinal cohort studies. Cancer registries have been in use in the UK and internationally for many years, whereas in rheumatology most registries have been developed only recently to monitor the new biologic therapies.

The term 'cohort' is used to describe a group of people who have something in common when they are first assembled. A cohort is usually established based on a specific diagnosis, and individuals may be recruited either at the time of diagnosis ('inception') or any time in the course of their disease ('prospective'). They are often referred to as long-term observational studies and used to describe and record the course and long-term complications of disease and its therapy. Ideally, they should be inception cohorts and provide assessments at specific and regular time-points for prolonged periods with as complete follow-up as possible.

Patient registries and cohort studies are very different from clinical trials in terms of design, logistics, approvals and site expectations. Success demands different expertise and core competencies. The main evidence for the efficacy and safety of medical products and therapies are provided by well-conducted randomized controlled trials (RCTs), considered the 'gold standard' research method. They generally study carefully selected groups of patients under controlled conditions, possibly over periods of months but not years. In a world of limited resources and patients with diverse risk factors and health conditions, clinicians, patients and commissioners need to know which products and services are safer, more effective and adhered to in a variety of 'true-to-life' settings that reflect the populations of interest, in both the short- and the long-term. Longer follow-up is possible through open-label extensions of RCTs, but these again include positive selections of patients originating from the trials.

Registries and cohort studies imply different processes to each other, and although they usually have different aims and designs, many ultimately come to resemble one another closely since most examine chronic conditions requiring prolonged follow-up. Most are related to conditions responsible for the bulk of follow-up in clinical rheumatology, namely adult inflammatory arthritis (AIA) and its subset rheumatoid arthritis (RA). Many have been designed for multiple purposes and not confined necessarily to answer just one research question. This article will examine the rationale, content and results of both registries and cohort studies for RA in the UK, although the principles and conclusions could apply to any medical field. Space restricts detailed inclusion of the many European and USA registries and cohort studies, which will be the subject of a future article.

Rationale for registries & cohort studies

Whether disease-based or product-focused, registries and cohort studies have been designed to capture data and evidence for both scientific and clinical governance issues. They provide the health community with invaluable data about the natural history of a disease or intervention under standard care practices, over periods that cover the development of most disease patterns and/or drug effects. Most aspire to regional if

not national coverage and many are voluntary. Clinical registries or cohort studies designed to capture operational clinical data as part of routine clinical care have the potential to promote better quality of treatment in general and in the individual patient, and specifically provide:

- Prevalence and incidence figures, geographical variations and secular change;
- Drug safety and benefit–risk data;
- Clinical guidelines and quality of care: development, improvement, monitoring and adherence;
- Health-related outcomes, including quality of life;
- Clinical and cost–effectiveness;
- Immediate access to well-presented longitudinal patient records generated from little additional work for the clinician;
- Data for research questions and, with time, a powerful research database.

The medical care costs of chronic diseases account for most of the National Health Service (NHS) budget, and some of the more common ones covered by national registries, for example cancer and diabetes. Registries are being increasingly developed for novel interventions, for example drug products, such as the biologic agents.

Currently, the most common registries in rheumatology are the Biologic Registries, developed in European countries since the introduction in 2001 of the new, more effective and expensive TNF-blocking agents for a number of autoimmune inflammatory conditions. At this time, the main clinical issues were not efficacy or short-term toxicity, which were not disputed, but were safety in the long-term and the choice of when the optimal stage of RA to introduce these novel agents was. The main reason for their initiation was because data on the long-term intended and unintended effects of biologics were relatively scarce. There were theoretical reasons to suspect that patients on biologics have increased risk of both malignancies (especially lympho-proliferative) and opportunistic infections over time. Another reason in some countries was the requirement to register patients prior to securing funding for these agents. Initially the clinical criteria for eligibility for biologics varied between countries, although agreement has now been achieved in Europe [1]. Registries have the potential for improving the understanding efficacy of therapies in the long-term, and provide information on whether a specific drug is clinically effective in real-world situations.

Registries can be associated with pay-for-performance quality-based contracts for individual, groups of or all doctors in a country. For example, the UK now rewards physicians according to 146 quality measures related to ten chronic diseases that are tracked electronically, and linked to the best-practice tariff.

In the USA, many registries are for surgical procedures or devices to monitor both long-term efficacy and healthcare expenses. The UK, Norway, Sweden and Australia have national patient registries that track patients with artificial joints in order to assess performance over time. Regulators can use such information to force manufacturers to justify why poorly performing hip or knee prostheses should remain available, and products have been withdrawn as a result.

Ethical issues vary according to individual national laws. Generally, no ethical approval is needed for the publication of the results of clinical audits that are based on routine collection of data. Research and other projects involving linkage to other registries or biobanks require ethical approval. Registries generally clear their methodology with data protection agencies, which are based on the Act of Processing of Personal Data that ensures that data security and protection of individual rights, among others, are dealt with correctly.

Historical account of registries & prospective cohorts of RA in the UK

The early population-based studies in the UK and USA in the 1950s–1960s provided data concerning the prevalence of RA and rheumatoid factor (RF) [2–4]. The findings suggested that self-limited polyarthritis was more common than progressive RA in general populations. RA inception cohorts in clinical settings followed, initially in the UK in the 1960s [5,6]. These cohorts provided, for the first time, valuable information on the course of hospital-based RA as they included strategies to follow-up the majority of patients using the same standard observations for at least 5 years. From these it became recognized that RA in the clinical setting differed from population studies. A far higher proportion of these patients had progressive

disease, supporting clinical experience. These differences were not widely recognized until the 1970s–1980s when these studies had sufficient follow-up to report the wide spectrum of RA. Unfavorable outcomes were reported early on in the disease course and, in significant proportions, were irreversible, resulting in questioning of management strategies.

Therapies at this time were limited to steroids and NSAIDs, and a small number of slow-acting disease-modifying antirheumatic drugs (DMARDs). The more effective agents, such as intramuscular gold and D-penicillamine, had significant and sometimes severe toxicity, so the need for reliable predictors of severe RA became increasingly more important.

At this time, no single marker or set of markers could be used to predict with certainty which patients were most likely to fare worse. The initial cohorts were disadvantaged by being single site and tertiary referral centers with limited numbers at follow-up, and not all assessments had been standardized. Scientific data from observational studies were not well regarded compared with randomized studies at this time, and it took several more years before it was recognized that if well designed and performed to a high standard, inception cohorts can provide clinical effectiveness and prognostic data to complement the results of RCTs [7].

Possible sources of bias in inception cohorts include small sample sizes at follow-up, left censoring (milder RA not being referred), right censoring (severe RA not surviving long enough for follow-up), and treatment effects. Assessment of therapies is limited in observational studies with nonrandom assignment of drug therapy. Study of drug efficacy is more reliably achieved with RCTs. However, newer agents can only be described as disease-modifying if demonstrated to alter objective measures in the long-term, namely x-ray damage. However, inception cohorts may permit comparison of the broader issue of clinical effectiveness of conventional and newer drugs in well-described historical cohorts.

A small number of single and multicenter hospital- and community-based inception observational cohorts in RA were designed in the UK and northern Europe in the 1980s in order to address these issues. With greater numbers at follow-up, some cohorts included the less common but important outcomes of clinical remission, work disability and orthopedic intervention. By the late 1990s most countries in northern Europe had established inception cohorts.

Most cohorts continue in follow-up, providing valuable comparative data on variations in therapeutic practice as well as other outcomes. Accumulated evidence from all RA inception cohorts has suggested that the course of the disease is highly variable, but is established early and that the most important phase for therapy is in the first 2 years. Most, but not all, have reported increased mortality compared with normal populations, mainly from cardiovascular disease. These factors were the main drivers for a more focused approach to the management of early RA.

Since the initiation of these cohorts, several major epidemiological advances in RA have been achieved in the last 15 years and included the revised classification criteria for RA [8], core sets of disease activity (DAS) measures [9], response criteria for the assessment of drug efficacy [10], and agreement on a core set of measures for longitudinal observational studies [11]. Another important development has been the formation of patient support groups in rheumatology. In the UK, both the National Rheumatoid Arthritis Society and the Arthritis and Musculoskeletal Alliance have become active not only politically, but have also contributed to the formation and running of studies and interpretation of results [101,102].

An important advance of the 1990s was evidence to support early intervention with disease-modifying therapies in RA [12]. This, and the success of inception cohorts, just described above, led to the development of early arthritis clinics, which are now part of standard services in many rheumatology departments. One challenge in establishing early arthritis clinics is to collect data continuously during routine care when patients are seen for the first time, or to have a clinical research facility attached to the clinical unit with the capacity to perform immediate on-demand data collection [13].

The more effective and expensive biological agents became available at the start of the millennium and this major therapeutic development resulted in the formation of product registries in the UK and many European countries including The Netherlands, Sweden, Norway, Denmark, France, Germany and Spain in order to monitor long-term adverse effects. The British Society of Rheumatology (BSR) established

the first Biologics Register (BSR-BR) in 2001 providing invaluable data on these agents in several disease areas, and the model for similar registries in other specialties, for example dermatology [14].

Details of the main RA cohorts & biologic registries

Table 1 summarizes the basic details of RA cohorts and registries initiated in the UK from the late 1950s that have stood the test of time and have reported on important outcomes with adequate follow-up. These are also described in detail below, followed by brief descriptions of the more recent initiatives not in the table.

Bath cohort

The first hospital-based early RA cohort recruited patients at the Royal National Hospital for Rheumatic Diseases in Bath, UK, between 1957 and 1963, and included 100 patients who met the American Rhematology Association criteria for definite or classical RA [15] and were first seen within 1 year of their initial arthritis symptoms prior to disease-modifying therapy [5]. Follow-up of these patients continued for up to 40 years and, although limited by progressively smaller numbers for analysis, it was the first to report a significant decline in functional capacity in as many as a third of the patients over the first 3 years, as well as high disability rates in the longer term.

The Middlesex Hospital cohort

The RAPS study was established in 1966 at Middlesex Hospital (London, UK) and enrolled consecutive patients with the same entry criteria as the Bath study, except that wider American Rheumatology Association criteria for RA were accepted to include less severe RA. The aim was to gather detailed information on the characteristics of disease onset in 100 patients in order to develop prognostic factors [6,16]. A novel finding was that serial x-rays of hands and feet demonstrated early changes, and nearly a third had structural damage by 1 year, rising to 71% by 5 years [17]. A subgroup of erosive patients was identified in whom no new erosions developed or progressed after approximately 3 years. This study was the first to show the importance of foot involvement in early RA, both clinically and radiographically

Only a few standardized and validated assessments were available to these first two cohorts and sample sizes were small, but they did achieve 15–25 years follow-up, and provided insights into early RA, which in this era was treated relatively late, mainly with intramuscular gold therapy as the first disease-modifying drug. Both demonstrated considerable fluctuation in the course of early RA and introduced the importance of serial follow-up of functional measures and x-rays of hands and feet.

The ERAS study

In the UK the proposal for a new inception cohort of RA arose from the recognition by a group of clinical rheumatologists in the 1980s that the optimal management for RA was a major challenge and any improvements were unlikely to result from RCTs alone. Important advances in the care of RA from the 1980–1990s included new drug therapies and standardized disease assessments. Large joint replacement surgery had become more routine and available. In order to develop prognostic factors and to capture the wide variations in clinical outcomes and health status, and in therapies offered in clinical practice, larger numbers of patients were required than hitherto possible.

The ERAS study was designed to recruit RA patients from NHS hospital rheumatology outpatients in nine different regions of England from 1986: a modernized version of RAPS. The aims were to establish a database of long-term clinical data on 1000 patients in order to monitor and compare management and outcomes between centers, and develop prognostic factors. Standard clinical assessments by research nurses included DAS, function (Health Assessment Questionnaire) and x-rays of hands and feet at baseline, 6 months and yearly for up to 20 years. Outcomes included validated assessments of functional and radiological progression, and mortality and comorbidity, with greater numbers and an improved management era compared with earlier cohorts [18]. The larger sample size allowed examination of both standard and less well-documented outcomes, which included clinical remission, work disability and orthopedic interventions (joint replacement and reconstruction) in RA patients treated with conventional DMARDs of the era [19–21]. Sulphasalazine was the first-choice DMARD of clinicians in this study, followed by methotrexate and intramuscular gold, which reflected common UK practice of this era. Severe toxicity from these conventional

Table 1. UK Cohort/registries with years of follow-up and publications.

Cohort	Location	Type of cohort	Recruitment	Maximum follow-up	Sample	Inclusion criteria	DAS	HAQ	QoL	Radiographic	Genetic	Comorbidity	Surgery	Ref.
Bath cohort	Bath	Inception	1957–1963	40 years	100	ARA, symptoms <1 year	No	No	No	Yes	No	No	No	[5]
RAPS	London	Inception	1966–1971	20 years	102	ARA, symptoms <2 years	No	No	No	Yes	No	No	No	[6]
ERAS	Multicenter	Inception	1986–2001	25 years	1465	Physician, symptoms <2 years	Yes	Yes	Yes	Yes	Yes	Yes	Yes	[18]
NOAR	Norfolk	Inception	1989–present	Ongoing	1657	Physician	Yes	Yes	Yes	Yes	Yes	Yes	No	[24]
ERAN	Multicenter	Inception	2001–2012	11 years	1236	Physician, symptoms <3 years	Yes	Yes	Yes	Yes	Yes	Yes	Yes	[30]
GORA	Sheffield	Cross-sectional	1999–2006	NA	873	Physician, symptoms <3 years	Yes	Yes	No	Yes	Yes	No	No	[110]
BSR-BR	Manchester	Registry	2001–present	Ongoing	~20,000	Physician, starting biologics	Yes	Yes	Yes	No	No	Yes	No	[43]
YEAR	Yorkshire	Inception	Cohort B: 1998–2003; Cohort C: 2000–2009	15 years	~1600	Physician, symptoms <1 years	Yes	Yes	Yes	Yes	No	Yes	No	[49]
BRAGGS	Multicenter	Prospective	2009–present	Ongoing	2520	Physician	No	No	No	No	Yes	No	No	[109]
CARA	Scotland	Prospective	2005–2006	1 year	465	Physician	Yes	Yes	Yes	No	No	Yes	No	[111]
RAMS	Multicenter	Inception	2008–2013	Ongoing	1100	Physician	Yes	Yes	Yes	Yes	No	Yes	No	[112]

ARA: American Rheumatology Association; DAS: Disease activity; HAQ: Health Assessment Questionnaire; NA: Not applicable; QoL: Quality of life.

DMARDs was uncommon, and very rarely related to mortality, which was more probable from nonsteroidal and steroidal drugs [22].

This study demonstrated that it was possible to collect standardized assessments in ordinary clinical settings over time without huge expense. However, despite a larger sample size, predictive markers powerful enough to be used routinely in clinical settings remained elusive. The power and relevance of predictive factors depended considerably on the outcome measure of interest, although RF remained consistent for most outcomes except function [23].

The Norfolk Arthritis Registry

NOAR [24] is a community-based study in one region of the UK designed to establish the incidence of inflammatory polyarthritis and RA in the 1990s [25], following on from the population studies conducted mainly in the industrial north of the UK in the 1950s. Patients recruited between 1989 and 1994 and between 2000 and 2008 in Norfolk were clinically assessed at baseline and at 1, 2, 3, 5, 7, 10 and 15 years by community research nurses. Patients recruited between 1994 and 2000 were followed for 2 years. NOAR reported an overall minimum prevalence of 1.16% in women and 0.44% in men [26] and, in comparison with the first UK studies in the 1960s [2,3], it was evident that prevalence in women was decreasing in all age groups (except in the 75+ group) whereas the prevalence in men has increased.

This study reported that even patients with AIA have unfavorable outcomes, significant morbidity and functional loss [27]. Patients who developed RA were followed-up in secondary care as a cohort study, and in these patients NOAR has reported on similar outcomes as ERAS. It is one of only a few UK studies that collected information on direct, indirect and intangible costs of the disease, based on specially designed questionnaires to capture costs of the disease from a personal, NHS and societal perspective [28].

Both NOAR and ERAS confirmed the finding of previous cohorts of irreversible disease in significant proportions of patients within the first few years. Despite improved therapies, reduced function early on was associated with later disability. Both studies took advantage of linkage to national datasets and reported increased standard mortality rates in RA [22,29]. The causes of

death in patients with RA were similar to that of the normal population, although infectious, cardiovascular and respiratory conditions were more common. These two cohorts represent the full spectrum of RA, and some differences in the results could be explained by generally milder RA from community sources compared with hospital-based patients.

The Early Rheumatoid Arthritis Network

The 21st century brought in a number of relevant developments: international and national guidelines on the management of RA had been published; patient support groups had become well organized and proactive; equitable access to appropriate care had become a greater issue in rheumatology. It was recognized that the introduction of clinical governance within the NHS had created a need for the collation of data on activity, contemporary treatment patterns and outcomes at national, as well as at local levels. Such data were required to facilitate planning and provision of healthcare for RA patients, and to inform the development of appropriate and realistic standards against which future activity could be audited.

ERAN had similar aims, design, and clinical assessments and outcome measures as ERAS, which ceased recruiting in 1999, but in a wider geographical area that included more centers. ERAN also had the intent to contribute to the development of good clinical practice, guidelines and clinical governance issues, and the added facility to conduct nested studies. ERAN recruited patients between 2002 and 2012 from 23 UK centers and was the first to report the variations in clinical management in the UK in the biologic era [30]. Follow-up data from this cohort provided data to support the BSR view that eligibility criteria for the initiation of biologics may have been set too high by NICE guidance [31], and that even patients with 'moderate' disease do badly within the first few years [32].

ERAS and ERAN are the only RA cohorts that reflect clinical practice in different regions of the UK prior to and during the biologic era, with data on 5–20-year outcomes. Strengths include a rapid reporting system of feedback loops with participating centers, allowing review of individual performance and comparison with national guidelines, and in some centers there was evidence of change in practice [33]. Recruitment fluctuated at certain times because some ERAN centers were not always able to recruit sequential patients, and some centers opted to stop recruiting new patients once a critical mass was achieved for that center in order to concentrate resources on follow-up. This is not an uncommon event in observational studies. Occurance of missing data was generally low and acceptable, but highest in drug start and stop dates (10%).

Combining the two cohorts has allowed examination of secular change in management of RA from 1986 to the present. This analysis has demonstrated several important trends: the earlier use of DMARDs once referred into secondary care; changes to the recommended practice of more intensive approaches in drug therapies in early RA in the UK has been slower than generally perceived and expected [33]; with improving therapies there has been the expected decline in orthopedic interventions, but only in reconstructive surgery of hands and feet, and not in large joint replacement arthroplasties (mainly hip and knees) [34].

Summary of results from UK inception cohorts

The early hospital-based inception cohort studies of the 1980s in the UK, Sweden and The Netherlands broadened the spectrum of RA following the pioneering population-based research in the UK of Kellgren and Lawrence in the 1950s and explained the discrepancy between the two approaches. These cohorts have provided valuable information on the natural (but treated) history of early RA and insights into the etiology, pathogenesis and outcomes of RA. They identified the significant proportion of patients who exhibited serious complications of RA at early stages of disease, not necessarily in those with conventional clinical features of moderate-to-severe disease. Measures of function (Health Assessment Questionnaire and work disability), structural damage (serial x-rays and orthopedic surgery) and morbidity and mortality have now become standard outcomes in RCTs, registries and cohort studies. Some of the subsequent north European cohorts have been multicenter with larger sample sizes, allowing subgroup analysis and, most importantly, had more complete and longer follow-up. They confirmed, refined and widened the earlier findings, highlighting the importance of both standardized and validated assessments, and the inclusion of all important outcome measures [35].

Several studies have provided important information on clinical effectiveness of disease-modifying therapies over time in the real world, which RCTs cannot do, and also on treatment variations, both regionally and between countries. Identifying the optimal management of RA still remains the most important challenge for clinical rheumatology. The BSR has used these data to inform published guidelines on management of RA in the 21st century [36,37].

At present optimal management depends on the use of best clinical practice/guidelines currently available, translating results of research studies into routine clinical practice, and identifying patients with poor prognostic factors and inadequate responses to initial therapies. The main UK cohorts identified the degree of delay from, first, onset of symptoms to hospital referral and, second, to start of disease-modifying therapies, and the possibility of improving on this. In the 1960–1970s patients were managed with NSAIDs for up to 2 years, often by primary care physicians, and slow-acting disease-modifying drugs only started in secondary care once erosions had developed. During this interval it was now postulated that the optimal window of opportunity to treat RA inflammation may be lost. By the 1980s, rheumatologists from the USA were advocating earlier intervention, based on clinical experience and small prospective studies [38]. Referral times into secondary care in the UK have improved only minimally over the last 20 years, the main delay being patient self-referral to primary care. Time to initiation of disease-modifying therapies once in secondary care has improved (from a median of 2 months to less than a month), although use of intensive therapies at outset was lower than expected [33].

The National Audit Office (NAO; London, UK) used extensive data from ERAS, ERAN and NOAR in their report on RA, commissioned by parliament in 2008 that highlighted these variations in current clinical practice and the disappointing outcomes, a key resource used in the HM Government Public Accounts Committee (tenth report published in 2010) [39]. Extensive use was made of the NAO report in subsequent NICE guidelines [103]. The profile of RA had certainly been raised by the NAO report [104], along with the availability and health economic issues surrounding the expensive biologics, ultimately to the benefit of patients. NICE guidelines for eligibility for funding of biologics include specific clinical criteria that are based on health economic analysis as well as clinical evidence [105] and are more stringent compared with the rest of Europe [31]. These issues will need further exploration in UK cohorts and registries, as long as they continue and provide contemporary data.

The current therapeutic 'treat-to-target' strategies for RA have demonstrated improvements in radiological change [40], but need to show consistent improvements in two other important outcomes: function and mortality. Age, sex and functional ability are the most consistent risk factors reported for mortality in these RA studies, followed by RF and acute phase response [22,29], supporting other evidence that the inflammatory process itself may play an important role in the development of ischemic heart disease. This is an important area as it raises the possibility of specific interventions to reduce mortality in RA. The beneficial effects of the more intensive therapies on mortality in RA are not yet proven, but these studies highlight the need for rheumatologists to treat RA patients with active disease early and effectively, identify those at risk from coexisting conditions and treat them actively or with preventative measures accordingly [41]. Pulmonary fibrosis is a well-recognized extra-articular feature of RA and poses an uncommon but severe risk, since this condition was responsible for 6% of deaths in one cohort [22]. This report prompted the formation of a register of RA-associated interstitial lung disease by rheumatologists in the UK to explore the course and predictive factors of this condition and possible therapeutic approaches to improve the poor prognosis [42].

UK product registries

The BSR-BR was set up to register all patients with RA newly starting biologic therapy from January 2002 [14]. The project includes a comparison cohort of RA patients treated with standard DMARDs. The registry records basic demographic characteristics including disease duration, function, DAS and associated European League for Arthritis and Rheumatism response, adverse events and quality-of-life scores, at baseline and at 6-monthly intervals for 3 years [43]. It now has data on several thousands of patients, estimated at 80% of patients starting DMARDs. The project was powered to detect a twofold increased risk in lymphoma, its primary aim, as RA patients already carry an increased

risk of lymphomas, thought to be linked to the abnormal immune system in RA. Biologics have a profound effect on immune mechanisms, so it has been reassuring that BSR-BR found no increased risk, although nonmelanoma skin cancers and opportunistic infections such as tuberculosis were increased [44]. The registry has been expanded to include patients with psoriatic arthritis and ankylosing spondylitis on biologics.

The results of BSR-BR and other national biologic registers in Europe have provided important evidence for evaluations of not only efficacy and toxicity, but also regional variations in the access and use of biologics. The BSR-BR has been able to answer its primary aim concerning the risk of lymphoproliferative conditions because this study had a control group of biologic-naive RA patients treated with conventional DMARDs. After more than 10 years of widespread use, it is still debated whether treatment with biologic agents is associated with an increase in solid tumor cancer incidence, and longer follow-up linked to independent cancer registers is needed. A meta-analysis reported no overall increase compared with nonbiologic treated RA [45]. The main drawback of biologic registries is expense due to labor-intensive data entry methodology and processes to minimize nonmissing data sets. One solution is to improve operational data capture methods by convincing clinicians and/or health professionals to engage at this level by recording data at the point of clinical contact. Another limitation of biologic registries is in the interpretation of drug efficacy, owing to nonrandomization of therapies. Misleading results may arise from channeling bias and confounding by indication, as well as variations in data quality of influences such as comorbidity.

The National Joint Registry (NJR) of England and Wales was established in 2002 to monitor, define, improve and maintain the quality of care of individuals receiving hip, knee and ankle joint replacement surgery across the NHS and the independent healthcare sector [106]. In 2008, the NJR was incorporated into the National Clinical Audit and Patients' Outcomes Program, both managed by the Healthcare Quality Improvement Partnership. The NJR is funded through a levy raised on the sale of hip, knee and ankle replacement implants available and used in the NHS and independent healthcare sectors across England and Wales.

■ Data linkage

The association between biologic-treated patients and lymphoma was made possible following data linkage with national databases, including the Cancer Registries, and mortality data from the Medical Research Information Service [107]. A number of other national databases in the UK provide invaluable data for cohort studies linked by NHS numbers. These include NHS hospital-based interventions from hospital episode statistics and the NJR [108], the General Practice Research Database, a primary care research databank started in 1987 covering 7% of the UK population (a proportion that is increasing) [46], and the NJR [106].

Several other important findings have resulted from linkage between separate and often quite different databases. For example, linkage between two unique registries, the NOAR and EPIC databases, revealed possible links between diet and the development of inflammatory arthritis in Norfolk [47]. Another example was the high incidence of pancreatic cancer in patients with RA exposed to leflunomide, which was observed in the German biologics register [48]. A concerted analysis with the national biologics registers in the UK and Sweden was performed, and the results of the replication analyses did not support the original finding [48]. Orthopedic surgery in RA is considered a surrogate marker for structural damage, not normally measured in large joints in cohort studies, and linkage of two consecutive RA inception cohorts with Hospital Episode Statistics and NJR has allowed an analysis of the frequency of and prognostic factors for this outcome. ERAS and ERAN cover the management of RA in the UK from 1986 to 2012 and demonstrated that over 20 years only certain types of orthopedic surgical rates have declined over this time [34]. The reasons for this are speculative, but highlight the problem associated with the interpretation of other long-term outcomes that are subject to variable and both modifiable and nonmodifiable influences, for example, mortality and work disability.

Other UK RA cohorts & registries recently initiated and/or that have limited publications

■ BRAGGS

Prospective cohort of RA patients from 49 clinical and academic centers in England designed

to collect clinical information and biologic and genetic samples from patients being treated with biologic drugs, in order to investigate treatment response predictors [109].

GORA

Genetic study in Sheffield (UK) that started in 1938, currently comparing genetic samples of established RA patients with controls [110].

Yorkshire Early Arthritis Register

An inception cohort for AIA (American College of Rheumatology criteria) followed yearly was set up in Leeds (UK) to cover NHS hospitals in Yorkshire, from 1998 to 2003 (Year B; 14 centers) and 2000–2009 (Year C; eight centers) [49].

Clinical Audit of RA

Initiated in Scotland in 2005 in eight centers to monitor management of early RA mainly as an audit exercise, from 2005–2008 [111].

RA methotrexate study

A recent initiative to collect and monitor data on physician diagnosis of RA or early undifferentiated polyarthritis, about to start methotrexate as monotherapy or in combination with other DMARDs for the first time. Included 32 centers between 2008 and 2013 [112].

RA-MAP

A recent initiative to identify predictors of remission in RA using patient-level data from patients who were either in the placebo arm of recently published RCTs examining nonbiologic DMARDs or biological agents, or in a longitudinal observational cohort in the UK designed to generate a model to predict remission. Sponsored by the Association of the British Pharmaceutical Industry (London, UK) and Arthritis Research UK (Derbyshire, UK). Includes a literature review; inventory of all RCTs and long-term observational studies in patients with RA that have remission among their outcome measures; and a survey to map cohort characteristics (size, entry criteria, baseline data, duration of follow-up, clinical and other end points, comparator and control/placebo treatments) [113].

MATURA consortium

A culmination of several separate initiatives with the primary aim to identify biomarkers (to include genetic and genomic tissue responses) in order to stratify medicines for RA to enable patients to be treated with the drug they are most likely to respond to earlier in their disease course. It builds on and complements other Medical Research Council-funded cohorts including the Pathobiology of Early Arthritis Cohort [114], BRAGGS [109] and RA-MAP Consortia [113], and represents an ideal opportunity for rheumatologists to collaborate on several strategic national and international initiatives in 2013. It underscores the cooperative philosophy, aims and values in developing a national arthritis network, similar to the cancer network that enables high-quality research to be translated into patient benefit [113].

ARUK INBANK

The ARUK INBANK initiative will provide the musculoskeletal research community with web-based software for standardized clinical data collection (with linked biosamples) to facilitate rapid and efficient acquisition and sharing of high-quality data for research across a network of UK NHS collection centers from 2014. It is proposed to support collection of data once and data reuse for multiple purposes, including research, clinical management, clinical audit and so on. Several musculoskeletal disease areas are proposed: the first and exemplar initiative is the AIA Hub (to include RA), and subsequent Hub developments will include other subspecialties in rheumatology [115].

Non-UK longitudinal cohorts & registries

Several north European countries and the USA initiated inception cohorts in the late 1980s and 1990s with similar designs and aims as those in the UK. This article cannot do justice to the importance of these numerous studies in detail owing to limited space. However, these cohorts reported on the same outcomes and prognostic factors in the same timeframe as already discussed, expanding at national levels on similar findings. Some outcomes are less easy to compare owing to socioeconomic variations, for example those studies that collected data on work disability, while others have exposed significant differences concerning management issues. It became clear that several European countries were treating early RA with more intensive combination drug strategies and biologics than the UK. Most other European

countries now also have biologic registries, mainly in northern Europe, with many based on the BSR-BR model. The accumulated evidence from European registries confirms the relative safety of biologics in the long term, and that the initial fears of malignancy have not been justified, although risk of infection is higher than expected.

Conclusion & future perspective

The disease and product registries and cohort studies in RA in the UK have generally been successful and have largely achieved their initial declared aims, outlined in the rationale list shown earlier in the opening section. The extent to which cohort studies have benefited the rheumatology community is detailed elsewhere [33,50], most importantly by identifying 'early RA' as a critical phase of the disease, which has driven the agenda for improved management, and by defining important outcomes.

The impressive results from registries and cohort studies have readdressed the previous imbalance perceived between observational studies and RCTs [7]. RCTs are limited by inclusion and exclusion criteria and, owing to this selection bias, do not reflect the 'real' world, one of strengths of registries and cohort studies. Biologic registries may suffer from 'channeling bias' because inclusion is often based on the more severe end of the disease spectrum. Well-designed inception cohorts that recruit all consecutive patients based on specific diagnostic criteria minimize bias, but do depend on low attrition rates, which should be accounted for, at least by notifications of mortality. The latter is possible in the UK due to linkage to the National Death Register. Missing data is a common issue that should be reported and to some extent can be addressed with modern statistical methods.

An encouraging development is the much greater extent of meaningful collaborations than previously seen between clinicians involved in the current registries and inception cohorts in both the UK [51] and Europe [52] in order to validate and strengthen problem areas of research findings, clearly the future for rheumatology research. Despite the large numbers in the inception cohorts described, the development of powerful prognostic factors has been disappointing, lacking the robustness needed for routine standard practice. In fact, it is uncertain how the predictive factors rheumatologist have at present are being used. Genetic analysis in particular needs large numbers, and is only available by combining cohorts. Great faith is being put into the development of biomarkers to replicate the models used in cancer.

After several years of planning, a number of national initiatives involving registries/cohorts in the management of AIA and RA are at last coming to fruition, underpinned by collaborations between key consortia with sound track records, including genomics [109], pathobiology [114], clinical trials for remission with pooled clinical trial datasets [113], a stratified medicines project [116]. ARUK has invested in the development of the national platform of clinical data in rheumatology, INBANK, linked to a central archive of stored biological samples and to NHS data from both primary and secondary care, for the acquisition and sharing of high-quality data for research across the NHS [115]. The pilot is planned to commence in 2014 and will bring together all the national cohorts, registries and current initiatives in RA described above.

The initiatives described here in rheumatology could promote the long-held and laudable view of the National Institute of Health Research to offer all patients the opportunity to be involved in research if appropriate, and patients inputting their own data is not far away.

Rheumatologists have been in the forefront of observational research, and operational data capture methodology has been developed as bespoke systems in some rheumatology departments, but as yet not on a national basis. This will be needed in order to accommodate the many new and established initiatives described here. Convincing clinicians to become involved at this level is a major challenge. The future brings multipurpose, user-friendly and cost-effective databases that will accommodate the needs of busy clinicians, clinical audit requirements, research, quality standards and commissioners.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:

- ▪ of interest
- ▪▪ of considerable interest

1 Combe B, Landewe R, Lucas C *et al.* EULAR recommendations for the management of early arthritis: report of the Standing Committee of ESCISIT. *Ann. Rheum. Dis.* 66(1), 34–45 (2007).

2 Kellgren JH, Lawrence JS. Rheumatoid arthritis in a population sample. *Ann. Rheum. Dis.* 15, 1–11 (1956).

3 Lawrence JS, Bennett PH. Benign polyarthritis. *Ann. Rheum. Dis.* 19, 20–30 (1960).

4 Mikkelsen WM, Dodge H. A four year follow-up of suspected rheumatoid arthritis: the Tecumseh, Michigan, community health study. *Arthritis Rheum.* 12, 87–91 (1969).

5 Jacoby RK, Jayson MIV, Cosh JA. Onset, early stages, and prognosis of rheumatoid arthritis: a clinical study of 100 patients with 11-year follow-up. *Br. Med. J.* 2, 96–100 (1973).

6 Fleming A, Crown JM, Corbett M. Early rheumatoid disease: I. Onset. *Ann. Rheum. Dis.* 35, 357–360 (1976).

7 Barton S. Which clinical studies provide best evidence? *Br. Med. J.* 321, 255–256 (2000).

8 Arnett FC, Edworthy SM, Bloch DA *et al.* The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum.* 31, 315–312 (1988).

9 Felson DT, Anderson JJ, Boers M *et al.* American College of Rheumatology core set of disease activity measures for rheumatoid arthritis clinical trials. *Arthritis Rheum.* 36, 729–740 (1993).

10 Felson DT, Aderson JJ, Boers M *et al.* American College of Rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum.* 38, 727–735 (1995).

11 Wolfe F, Lassere M, van der Heijde D *et al.* Preliminary core set of domains and reporting requirements for longitudinal observational studies in rheumatology. *J. Rheumatol.* 26, 484–489 (1999).

12 van der Heijde D, Jacobs JW, Bijlsma JW *et al.* The effectiveness of early treatment with 'second-line' anti-rheumatic drugs. A randomized, controlled trial. *Ann. Intern. Med.* 124, 699–707 (1996).

▪ **One of the first well-designed randomized controlled trials to examine and demonstrate the value of early intervention in recent-onset rheumatoid arthritis (RA).**

13 Gough A, Young A, Bacon P. Setting up an early inflammatory arthritis clinic. In: *Management of Early Inflammatory Joint Disease*. Emery P (Ed.). Elsevier, Amsterdam, The Netherlands (1992).

14 Silman A, Symmons D, Scott DG, Griffiths I. British Society for Rheumatology Biologics Register. *Ann. Rheum. Dis.* 62(Suppl. 2), ii28–ii29 (2003).

15 Ropes MW, Bennett GA, Cobb S, Jacox RF, Jessar RA. 1958 revision of diagnostic criteria for rheumatoid arthritis. *Bull. Rheum. Dis.* 9, 175–176 (1958).

16 Young A, Corbett M, Winfield J *et al.* A prognostic index for erosive changes in the hands, feet, and cervical spines in early rheumatoid arthritis. *Br. J. Rheumatol.* 27, 94–101 (1988).

17 Brook A, Corbett M. Radiographic changes in early rheumatoid disease. *Ann. Rheum. Dis.* 36, 71–73 (1977).

18 Young A. Short term outcomes in recent onset rheumatoid arthritis. *Br. J. Rheumatol.* 34(Suppl. 2), 79–86 (1995).

19 Young A, Dixey J, Cox N *et al.* How does functional disability in early rheumatoid arthritis affect patients and their lives? Results of 5 year follow up in 781 patients from the Early RA Study (ERAS). *Rheumatology (Oxford)* 39, 603–611 (2000).

20 Young A, Dixey J, Kulininska E *et al.* Which patients with early RA stop working? Results from a 5 year inception cohort of 732 patients. *Ann. Rheum. Dis.* 61, 335–340 (2002).

21 James D, Young A, Kulinskaya E *et al.* Orthopaedic intervention in early rheumatoid arthritis. Occurrence and predictive factors in an inception cohort of 1029 patients followed for 5 years. *Rheumatology (Oxford)* 43, 369–376 (2004).

22 Young A, Koduri G, Batley M, Kulinskaya K, Gough A, Dixey J. Mortality in rheumatoid arthritis. Increased in the early course of disease, in ischaemic heart disease and pulmonary fibrosis. *Rheumatology (Oxford)* 46, 350–357 (2006).

▪ **One of the few hospital-based inception cohorts examining mortality rates and cause of death in RA in nine different regions of England, which included rural, urban and inner city socioeconomic variations. Standard mortality rates were increased in the first 7 years of RA.**

23 Young A, van der Heijde DF. Can we predict aggressive disease? In: *Early Rheumatoid Arthritis*. Woolf A, van Reil P (Eds). Elsevier, Amsterdam, The Netherlands, 11, 27–48 (1997).

24 Symmons DP, Silman AJ. The Norfolk Arthritis Register (NOAR). *Clin. Exp. Rheumatol.* 21(5 Suppl. 31), S94–S99 (2003).

25 Symmons DP, Barrett EM, Bankhead CR, Scott DG, Silman AJ. The incidence of rheumatoid arthritis in the United Kingdom: results from the Norfolk Arthritis Register. *Br. J. Rheumatol.* 33, 735–739 (1994).

26 Symmons D, Turner G, Webb R *et al.* The prevalence of rheumatoid arthritis: new estimates for a new century. *Rheumatology (Oxford)* 41, 793–800 (2002).

27 Wiles NJ, Dunn G, Barrett EM, Harrison BJ, Silman AJ, Symmons DP. One year follow up variables predict disability 5 years after presentation with inflammatory polyarthritis with greater accuracy than at baseline. *J. Rheumatol.* 27, 2360–2366 (2000).

28 Cooper NJ, Mugford M, Symmons DP, Barrett EM, Scott DG. Total costs and predictors of costs in individuals with early inflammatory polyarthritis: a community-based prospective study. *Rheumatology (Oxford)* 41(7), 767–774 (2002).

▪ **One of few cost-effective studies from RA inception cohorts, and highlighted the importance of community costs.**

29 Goodson NJ, Wiles NJ, Lunt M, Barrett EM, Silman A, Symmons DP. Mortality in early inflammatory polyarthritis. *Arthritis Rheum.* 2010–2019 (2002).

30 Kiely P, Williams R, Walsh D, Young A; for the Early Rheumatoid Arthritis (ERAN). Contemporary patterns of care and disease activity outcome in early rheumatoid arthritis: the ERAN cohort. *Rheumatology* 48, 57–60 (2009).

▪ **Only contemporary hospital-based inception cohort in the UK examining current patterns of care in RA in over 20 rheumatology units. The results have informed national bodies in deliberations concerning management of RA in the future.**

31 Deighton C, Hyrich K. Why do the French get much greater access to anti-TNF than the British? Vive la différence? Pas nécessairement. *Rheumatology* 47, 1600–1602 (2008).

▪ **Highlighted the difference in eligibility criteria for biologics for RA between the UK and the rest of Europe.**

32 Kiely P, Walsh D, Williams R, Young A. Outcome in RA patients with continued conventional therapy for moderate disease

activity. The Early Rheumatoid Arthritis Network (ERAN). *Rheumatology (Oxford)* 50(5), 926–931 (2011).

■ **Demonstrated that even patients with 'moderate' RA who are therefore ineligible for biologics could have poor outcomes.**

33 Young A, Dixie J, Williams P *et al.* An evaluation of the strengths and weaknesses of a register of newly diagnosed rheumatoid arthritis, 1986–2010. *Rheumatology (Oxford)* 50, 176–183 (2011).

■■ **Summary of two early RA registries in the UK that demonstrated that most therapeutic recommendations for good clinical practice in RA have been followed, but for some, the expected changes over time have been considerably slower than anticipated.**

34 Nikiphorou E, Carpenter L, Kiely P, Walsh D, Dixey J, Young A. Has orthopaedic intervention for rheumatoid arthritis changed in line with combination and anti-TNF therapies? An evaluation of joint surgery rates and prognostic factors in two UK inception cohorts (1986–2011). *Rheumatology* 51(Suppl. 3), iii27 (2012).

35 Curtis JR, Jain A, Askling J *et al.* A comparison of patient characteristics and outcomes in selected european and US rheumatoid arthritis registries. *Semin. Arthritis Rheum.* 40(1), 2–14 (2010).

36 Luqmani S, Hennell C, Estrach F *et al.*; on behalf of the British Society for Rheumatology and British Health Professionals in Rheumatology Standards, Guidelines and Audit Working Group British Society for Rheumatology and British Health Professionals in Rheumatology. Guideline for the management of rheumatoid arthritis (the first 2 years). *Rheumatology* 45, 1167–1169 (2006).

37 Luqmani R, Hennell S, Estrach C *et al.*; on behalf of the British Society for Rheumatology and British Health Professionals in Rheumatology Standards, Guidelines and Audit Working Group. British Society for Rheumatology and British Health Professionals in Rheumatology guideline for the management of rheumatoid arthritis (after the first 2 years). *Rheumatology* 48, 375–384 (2009).

38 Pincus T, Callahan L. Taking mortality in rheumatoid arthritis seriously – predictive markers, socio-economic status and comorbidity. *J. Rheumatol.* 13, 841–845 (1986).

39 National Audit Office. *Services for People with Rheumatoid Arthritis.* The Stationery Office, London, UK (2009).

40 Schoels M, Knevel R, Aletaha D *et al.* Evidence for treating rheumatoid arthritis to target: results of a systematic literature search. *Ann. Rheum. Dis.* 69, 638–643 (2010).

■■ **Provided the evidence to date of the value of targeted treatment schedules in achieving better outcomes in RA.**

41 Pincus T, Gibofsky A, Weinblatt ME. Urgent care and tighter control of rheumatoid arthritis as in diabetes and hypertension: better treatments but a shortage of rheumatologists. *Arthritis Rheum.* 46, 851–854 (2002).

42 Chan E, Saravanan V, Dawson J *et al.* Rheumatoid arthritis related interstitial lung disease – which factors predict its development? *Rheumatology (Oxford)* 52(Suppl. 1), ii75 (2013).

43 Watson K, Symmons D, Griffiths I, Silman A. The British Society for Rheumatology biologics register. *Ann. Rheum. Dis.* 64(Suppl. 4), iv42–iv43 (2005).

44 Dixon WG, Symmons DP, Lunt M, Watson KD, Hyrich KL, Silman AJ. Serious infection following anti-tumor necrosis factor α therapy in patients with rheumatoid arthritis: lessons from interpreting data from observational studies. *Arthritis Rheum.* 56, 2896–2904 (2007).

■ **Careful analysis of the British Society for Rheumatology Biologic Register showing that the occurrence of opportunistic infections was slightly increased in patients treated with biologics compared with controls, the most important being tuberculosis.**

45 Mariette X, Metucci-Cerinic M, Pavelka K *et al.* Malignancies associated with tumour necrosis factor inhibitors in registries and prospective observational studies: a systematic review and meta-analysis. *Ann. Rheum. Dis.* 70, 1895–1904 (2011).

46 Watson DJ, Rhodes T, Guess HA. All-cause mortality and vascular events among patients with rheumatoid arthritis, osteoarthritis, or no arthritis in the UK General Practice Research Database. *J. Rheumatol.* 30, 1196–1202 (2003).

47 Pattison DJ, Symmons DP, Lunt M *et al.* Vitamin C and the risk of developing inflammatory polyarthritis: prospective nested case–control study. *Ann. Rheum. Dis.* 63, 843–847 (2005).

48 Strangfeld A, Hyrich K, Askling J *et al.* Detection and evaluation of a drug safety signal concerning pancreatic cancer: lessons from a joint approach of three European biologics registers. *Rheumatology* 50, 146–115 (2011).

49 Morgan AW, Robinson JI, Conaghan PG *et al.*; UKRAG Consortium; YEAR Consortium. Evaluation of the rheumatoid arthritis susceptibility loci HLA-DRB1, PTPN22, OLIG3/TNFAIP3, STAT4 and TRAF1/C5 in an inception cohort. *Arthritis Res. Ther.* 12(2), R57 (2010).

50 Young A. What have we learnt from early RA cohorts? *Best Pract. Res. Clin. Rheumatol.* 23(1), 3–12 (2009).

■■ **Review and summary of the value of inception cohorts in RA.**

51 Norton S, Fu B, Verstappen SM *et al.* Common trajectories of HAQ disability progression over 15-years in the Early Rheumatoid Arthritis Study and the Norfolk Arthritis Register. *Ann. Rheum. Dis.* 71(Suppl. 3), 508 (2012).

52 van der Woude D, Young A, Jayakumar K *et al.* Prevalence of and predictive factors for sustained DMARD-free remission in RA; results from two large early arthritis cohorts. *Arthritis Rheum.* 60, 2262–2227 (2009).

■ Websites

101 National Rheumatoid Arthritis Society. Early Rheumatoid Arthritis Study. www.nras.org.uk/about_rheumatoid_arthritis/established_disease/new_developments_clinical_research/archive_clinical_research/early_rheumatoid_arthritis_study_eras.aspx

102 Arthritis and Musculoskeletal Alliance. http://arma.uk.net/wp-content/uploads/pdfs/ia06.pdf

103 NICE. www.nice.org.uk/usingguidance/commissioningguides/biologicaltherapies/home.jsp

104 National Audit Office. www.nao.org.uk

105 NICE. Adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis. www.nice.org.uk/nicemedia/pdf/ta130guidance.pdf

106 National Joint Registry of England, Wales and Northern Ireland. www.njrcentre.org.uk

107 Medical Research Information Service. http://webarchive.nationalarchives.gov.uk/20080814090357/ic.nhs.uk/our-services/improving-patient-care/medical-research-information-service

108 Hospital Episode Statistics online, 2011. www.hscic.gov.uk/hes

109 University of Manchester. Biologics in Rheumatoid Arthritis Genetics and Genomics Study Syndicate (BRAGGS). www.medicine.manchester.ac.uk/musculoskeletal/research/arc/genetics/pharmacogenetics/braggss

110 The University of Sheffield. www.shef.ac.uk/polopoly_fs/1.123251!/file/GORA-Newsletter.pdf

111 Healthcare improvement Scotland. Clinical Audit of Care in Rheumatoid Arthritis (CARA). www.healthcareimprovementscotland.org/previous_resources/audit_report/cara_rheumatoid_arthritis.aspx

112 RAMS. www.medicine.manchester.ac.uk/musculoskeletal/research/arc/clinicalepidemiology/pharmacoepidemiology

113 TACERA. www.gsttbrc.com/tacera/..%5CTACERA%5CPatInfoDocs/TACERA%20Protocol%20-%20Version%202.0%20-%2029.05.2012.pdf

114 Medical Research Council. Pathobiology of Early Arthritis Cohort (PEAC). www.peac-mrc.mds.qmul.ac.uk

115 Arthritis Research UK. INBANK. www.arthritisresearchuk.org/research/inbank.aspx

116 National Institute for Health Research. Biomedical Research Centres. www.nihr.ac.uk/infrastructure/Pages/infrastructure_biomedical_research_centres.aspx