REVIEW

Swedish registers to examine drug safety and clinical issues in RA

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Data from several different monitoring systems are examined. The potential for registers based on data obtained from clinical practice, and linkage of such data to national health and population registers, is discussed. The approach described is a possible prototype for long term surveillance systems needed for the safe introduction of new treatments.

It has become increasingly clear that randomised trials and spontaneous reporting of adverse events are insufficient instruments to detect uncommon, unexpected, or long term side effects of new drugs. This is particularly true for biological agents like tumour necrosis factor (TNF) antagonists, which exert their action through a pharmacologically new principle. Similarly, important clinical questions about effectiveness in routine use may never be subject(able) to testing in randomised trials. Other approaches to these issues are thus warranted. Recently, data from several different monitoring systems have been reported. In this review we discuss the potential for registers based on data retrieved from clinical practice, exemplified by our experiences with the profession based Swedish efforts to register and monitor rheumatoid arthritis (RA); investigate how such data may be linked to national health and population registers; and consider the diversity of clinical issues that may be examined by these registrations. We suggest that the described approach offers a prototype for the long term surveillance systems that are needed to permit safe and rational clinical use of the many new treatments that will be offered to rheumatology during coming years.

Pre-approval drug safety

Randomised controlled trials represent an efficient design to assess drug efficacy and to detect common, immediate, and predefined side effects. Cost, power, and logistics pose a limit to the possibility of identifying insidious side effects such as adverse events and changes in comorbidity patterns.[1] In contrast with a 1 year trial, for example, most responders in clinical practice may face decades of treatment. Likewise, even thousands of patients in a trial may be an inadequate sample for detecting hazardous, but rare, adverse effects. Also, patients receiving a drug in clinical practice differ from patients fulfilling the typical restrictive inclusion criteria of clinical trials.[2 3] Hence, at the time of drug approval, much safety assessment is still required.

Post-marketing drug safety

Post-marketing safety monitoring has traditionally been managed through passive surveillance systems reliant upon reporting by physicians, manufacturers, or others.[4] Unfortunately, underreporting to such systems is often considerable (What fraction of heart attacks in patients exposed to Cox 2 inhibitors were reported to the Federal Drug Administration (FDA) before October 2004?), information on the number of patients exposed to treatment is limited, and knowledge of the expected occurrence of the event in question among unexposed patients is often scarce.[5] Moreover, inherent in spontaneous reporting is the reporter's assumption that the reported event may represent an adverse reaction. Although the shortcomings of current post- (and pre-) approval safety surveillance have recently been highlighted by the actions taken against Cox 2 inhibitors, the problem of long term safety surveillance is general.[6 7] Indeed, without better systems, the introduction of new drugs risks becoming slower and more costly, and we are in danger of causing unjustified withdrawals and discouraging the development of new drugs that might deal with important unmet medical needs.

Key players

Who should be responsible for conducting such post-marketing safety programmes? Although regulatory agencies like the FDA and the European Medicines Agency (EMEA) do not have the means to conduct safety studies themselves, they are increasingly demanding this information as part of the approval process, often as part of a ''conditional approval'', under which a new drug is approved only if appropriate safety monitoring is conducted and results are reported to the drug agencies.[8] Regulatory guidelines for pharmacovigilance planning have recently been issued. Most often, the pharmaceutical companies are given the responsibility

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Abbreviations: ACR, American College of Rheumatology; ARTIS, Anti-rheumatic therapies in Sweden; CI, confidence interval; DAS28, 28 joint count Disease Activity Score; DMARDs, disease modifying antirheumatic drugs; HAQ, Health Assessment Questionnaire; MPA, Medical Products Agency; RA, rheumatoid arthritis; RR, relative risk; SSATG, South Swedish Anti-TNF Group Register; STURE, Stockholm Tumor Necrosis Factor-α Follow-up Registry; TNF, tumour necrosis factor; VAS, visual analogue scale

for providing data. The industry itself is, however, not the ideal institution to collect and analyse such data. Patients in clinical practice need to be monitored for many different drugs, often given simultaneously. Furthermore, comparator groups of patients with similar disease but who are receiving no—or different—treatment are required, in order to permit quantification of the risk of comorbidities occurring owing to the use of a particular drug. A single company responsible for the safety of one particular drug will be unable to deal appropriately with these tasks.

> ''The medical profession may be better placed than a single pharmaceutical company to monitor a drug's safety''

The solution may instead be to give the responsibility for collecting and analysing data to the medical profession, to provide the profession with appropriate resources to conduct such studies, to institute a system for audit of the quality of this endeavour, and to permit the pharmaceutical industry and regulatory authorities appropriate access to this information.

Keeping track of records, not just a safety issue

Besides drug safety, clinicians must develop strategies for rational and cost effective use of new drugs. Several such clinically important issues may neither be assessed by the pharmacological companies, nor lend themselves to testing in randomised trials.[9] Likewise, clinicians increasingly need a way of demonstrating the therapeutic effectiveness of new treatments in order to justify their cost to health providers. It is thus important that any system including monitoring of patients receiving new drugs also makes it possible to evaluate drug usage, treatment effectiveness, and functional measures.

SWEDISH MONITORING SYSTEM FOR BIOLOGICAL AGENTS

Efforts to establish drug registers which permit safety assessments and clinical studies are currently undertaken in many countries, with partially different goals and using different approaches.[10–16] These efforts should be seen as complementary rather than competitive. Over the past 7 years, we have established a profession based system for monitoring efficacy and safety of TNF blocking agents used against RA. The fundamentals of our system include a coordinated but non-mandatory effort by Swedish rheumatologists to enter data into a nationwide register, and a close collaboration between the rheumatology profession and the Swedish Medical Products Agency (MPA).

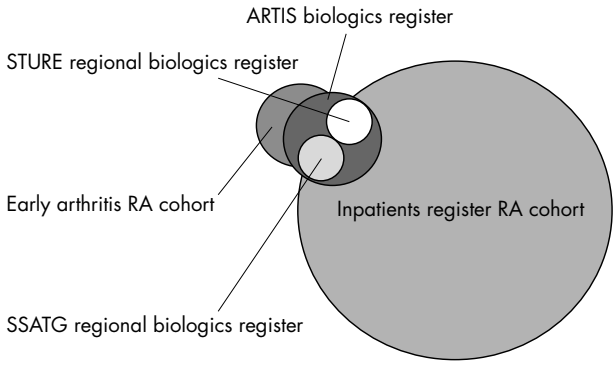

Figure 1 Swedish regional and national biologics RA cohorts, and comparator RA cohorts.

The Swedish setting

Sweden has a population of nine million inhabitants, half of whom live in metropolitan areas. Swedish health care is public and population based. Use of outpatient or inpatient care is not governed by private health insurance, but largely follows geographical referral patterns and is tax funded.[17] Patients with inflammatory rheumatic diseases such as RA are treated by rheumatologists rather than by general practitioners. Swedish care for RA represents a mix of combined outpatient and inpatient facilities, with most rheumatologists working at hospitals rather than as private practitioners.

Swedish registers of RA (fig 1)

Early Arthritis Register

The Early Arthritis Register, maintained by the Swedish Society for Rheumatology, is a longitudinal register of incident RA and has been in operation since the mid-1990s. The number of participating centres and their coverage has increased over time—in particular, after merging of the Early Arthritis Register with certain regional inception cohorts for RA (Swedish TIRA and BARFOT).[18 19] Participating centres represent a mix of small and large clinics or departments. Apart from date of diagnosis and the American College of Rheumatology (ACR) criteria at the time of diagnosis, data on disease activity and treatment are collected at prespecified intervals from the time of diagnosis (table 1). In practice, the initially paper based reporting to the register has been changed into a web based reporting that allows the reporting physician a graphical and tabular depiction of current and past disease activity and medication, information that should provide a tool in the clinical decision making process. At present, the register includes information about 5377 patients, with a maximum follow up from diagnosis of 8 years (table 2). Over 90% have at some point been prescribed disease modifying antirheumatic drugs (DMARDs), and around 15% have received biological agents.

Inpatient Register RA cohort

The Inpatient Register RA cohort is a cohort of prevalent patients with RA who have been admitted to hospital that is generated from the Swedish Inpatient Register (below). By searching the inpatient register for discharges listing RA as one of the discharge codes, subjects admitted to hospital with or because of their RA may be identified. Although all discharges (hospitals, departments, and dates) listing RA may be identified, there is no information on the exact date of onset or on treatment. To assess the accuracy of the diagnosis, the medical files of almost 1000 subjects admitted to hospital with a diagnosis of RA have been scrutinised.[20] Around 90% of these patients fulfilled the ACR criteria. As regards the generalisability, we estimate that the around 90 000 subjects with RA who can be identified in the inpatient register correspond to about 50% of all patients in Sweden today, assuming a true population prevalence of 0.7%. The high figure is explained not only by historically low thresholds for inpatient care for RA, but also by the fact that many subjects have their RA registered during inpatient episodes mainly related to other conditions (for example, delivery, other diseases, and surgery).

Swedish biologics registers

Since 1999, but before their market approval in 2000, TNF antagonists could be prescribed in Sweden for a named patient after approval by the MPA. Named patient prescription was permitted only if the prescribing physician agreed to participate in registration of effects and adverse effects of the drug. The ownership and overall responsibility for the resulting registry—named ARTIS—was assigned to the Swedish Rheumatology Association. After formal approval

Table 1 Schematic content of the Swedish Early Arthritis Register, the national ARTIS biologics cohort, and its two major subsets—namely, the SSATG and the STURE regional biologics registers

		ARTIS biologics register		
Schematic content	**Early arthritis**	**Total ARTIS cohort**	**STURE**	**SSATG**
At inclusion				
Age, sex	Yes	Yes	Yes	Yes
Diagnosis	Yes	Yes	Yes	Yes
Contributing diagnosis	No	No	No	Yes
Disease onset	Yes	Yes	Yes	Yes
ACR RA criteria	Yes	No	No	No
Follow up time points*	0, 3, 6, 12 and every 6 months	0, 3, 6, 12 and every 6 months	0, 3, 6, 12 and every 6 months	0, 3, 6, 12 and every 6 months
At follow up				
Prescribed drugs				
Biological agent (type and dose)	Yes†	Yes	Yes	Yes‡
DMARD (type)	Yes	Yes	Yes	Yes‡
Prednisolone (no/yes/dose)	Yes	Yes	Yes	Yes‡
NSAID/Coxib (no/yes)	Yes	Yes	Yes	Yes‡
Analgesics (no/yes)	Yes	Yes	Yes	Yes‡
Evaluated measures				
Tender and swollen 28 joint counts	Yes	Yes	Yes	Yes
VAS global	Yes	Yes	Yes	Yes
VAS pain	Yes	Yes	Yes	Yes
Global evaluator (5 point Lickert scale)	Yes	Yes	Yes	Yes
HAQ	Yes	Yes	Yes	Yes
EQ-5D	No	No	No	Yes
Working capacity	Yes	No	No	Optional
Health economic measures	No	No	No	Optional
Tender/swollen 66/68 joint count	No	No	No	Optional
Calculable measures§				
DAS28, and DAS28 activity level	Yes	Yes	Yes	Yes
EULAR response	Yes	Yes	Yes	Yes
ACR response	Yes	Yes	Yes	Yes
VAS global response	Yes	Yes	Yes	Yes
VAS pain response	Yes	Yes	Yes	Yes
HAQ response	Yes	Yes	Yes	Yes
Health utility values	No	No	No	Yes
Data handling				
Data entry	Decentralised	Decentralised	Decentralised	Centralised
Entry mode	Web	Web	Web	Paper form
Patient data entry	Optional	Optional	Optional	No
Primary data storage	National	National	Regional	Regional
Missing data requested	Yes	Yes	Yes	Yes (biannual)

*Any visit, whether scheduled or unscheduled, may be registered; †patients in the Early Arthritis Register who start treatment with biological agents are automatically flagged for the ARTIS register as both registers use the same data entry and storage facility; ‡includes information also on drugs *taken*; §*Online* for the treating physician ARTIS displays DAS, DAS response, and disease activity level, whereas SSATG displays all the calculable measures.

of the TNF antagonists, reporting of new patients starting treatment with the drug has continued.

Data are registered in ARTIS at the start of treatment with a biological agent, at regular visits during treatment, and when treatment ends (table 1). In addition, data on adverse events are entered as they occur or become known to the treating physician. Initially, data were entered on paper forms by the treating physician (one page for the physician, one page for the patient) and were then entered into the database centrally. Since 2003, data may also be entered directly through a web page which allows data entry and evaluation of patient performance during the patient's visit. As a consequence, an increasing proportion of doctors now report to the registry solely through the web. The web based reporting system (and the reported data elements) is identical to that used for reporting to the Early Arthritis Register (table 1). Quality control and help with data entry are provided by the staff at the ARTIS secretariat. Adverse events reported to ARTIS are channelled to the MPA and, if evaluated as serious by the agency, fed into the agency's conventional adverse events reporting system (SWEDIS). So far, ARTIS has resulted in a considerable increase in the number of events reported (with a defined denominator!) to the existing vigilance system.

There is one exception to the direct registration to ARTIS. In southern Sweden, covering 20% of the Swedish population, data on start/stop and regular visits for patients treated with biological agents are primarily recorded (on paper) to the South Swedish Anti-TNF Group Register (SSATG). Core data from the SSATG are subsequently entered into ARTIS through biannual data exports. Importantly, adverse events data are not exported biannually but channelled to ARTIS and the MPA as they are reported. Apart from data for ARTIS, the SSATG records some additional information (table 1). Likewise, in the greater Stockholm area, the STURE register makes use of the data reported to ARTIS. In contrast with the SSATG, STURE is not a physically separate register. Instead, the STURE subset of ARTIS might be better described as a population based framework for the testing of research hypotheses that necessitates focused collection of specific clinical data. Indeed, rather than competing systems of follow up, one of the advantages of our system is that mutual (national and regional) benefits from data registration are possible.

At present, in ARTIS a biological agent has been started on 9645 occasions among 7354 patients (table 2). A rough estimate against sales statistics indicates an overall coverage of ARTIS of around 80%, although this figure varies with period and region (for example, it is higher for areas covered by SSATG and STURE, which together make up half of ARTIS). Data completeness is high for the type of biological agent followed up, with few subjects (<1%) lacking

Table 2 Numbers included in Swedish Early Arthritis Register, the national ARTIS biologics cohort and its two major subsets—namely, the SSATG and the STURE regional biologics registers

		ARTIS biologics register		
	Early Arthritis Register	Total ARTIS cohort	STURE	SSATG
Patients entered (n)	5377*	7354	1999	2210
Treatments started, No (%)		9645 (100)	2745 (100)	2978 (100)
Enbrel	–	3585 (37.2)	1079 (39.3)	1182 (39.7)
Remicade	–	4027 (41.8)	1121 (40.8)	1130 (37.9)
Humira	–	1798 (18.6)	487 (17.7)	553 (18.6)
Other biological agents	–	235 (2.4)	58 (2.1)	113 (3.8)
Disease activity at entry†, mean (SD)				
DAS	5.18 (1.29)	5.30 (1.44)	5.34 (1.37)	5.30 (1.32)
HAQ	1.10 (0.58)	1.36 (0.64)	1.39 (0.64)	1.32 (0.66)
Disease duration at entry (years), mean (SD)	0.54 (0.25)	9.7 (10)	10 (10)	12.7 (10.6)
Entry periods, No (%) of patients				
Missing values	0	2 (0.03)	0	0
<1995	40 (0.7)	0	0	0
1995–1998	1109 (20.6)	38 (0.5)	22 (1.1)	2 (0.1)
1999–2001	1598 (29.7)	2663 (36.2)	657 (32.9)	884 (40.0)
2002–2003	1328 (24.7)	2155 (29.3)	606 (30.3)	583 (26.4)
2004–2005	1302 (24.2)	2496 (33.9)	714 (35.7)	739 (33.4)
Follow up, No (%) subjects who have accrued				
Missing values	5 (0.1)	18 (0.2)	5 (0.3)	2 (0.1)
<1 year	818 (15.2)	2369 (32.2)	688 (34.4)	600 (27.1)
1–3 years	2252 (41.9)	3472 (47.2)	972 (48.6)	970 (43.9)
4–5 years	1061 (19.7)	957 (13.0)	222 (11.1)	439 (19.9)
6+ years	1241 (23.1)	538 (7.3)	112 (5.6)	199 (9.0)

*Patients in the Early Arthritis Register who start treatment with biological agents are automatically flagged for the ARTIS register as both registers use the same data entry and storage facility.
Data as of December 2005.

information. Because of the real life setting, losses to follow up are somewhat difficult to separate from subjects with overdue visits or visits not yet registered. The cumulative proportion of patients in ARTIS who up until 2005 had their last registered visit more than 6 months behind schedule and had no notification of treatment termination was 12%. The corresponding figures for STURE and the SSATG are lower (<5%).

Methods of follow up, outcome ascertainment, and comparison of data

Because of the decentralised data input into ARTIS and the availability of national registers for independent follow up and outcome ascertainment, follow up for vital status and the kind of outcomes that define serious adverse events (hospitalisations, cancers, deaths, malformations) in ARTIS does not require regular contacts, but may be achieved through register linkages. Dropouts from ARTIS, SSATG, STURE or from the Early Arthritis Register should therefore be thought of as missing information on exposure rather than as losses to follow up, and does not preclude the register based detection of outcome—for example, a later lymphoma. Because of the availability of already defined RA cohorts (see above) that may be subjected to the same follow up, we have not set out to create a physical comparator cohort specifically for ARTIS. (In contrast with other countries—for example, the UK, use of biological agents in Sweden has never been restricted by health authorities. As a consequence, the possibility of identifying a biologics-naive comparator of qualitatively and quantitatively equal accumulated and acute disease activity is more limited.) Instead, using register linkages, we have specified outcomes and compared their occurrence in the biologics cohorts with that in the other and pre-existing RA cohorts.

Follow up and outcome registers

Up until now, we have used the following nationwide registers:

Total Population Register This includes data on residency at a given point in time (1961–2003), and dates of emigration/immigration for all subjects ever resident in Sweden during this interval.

Cause-of-Death Register This provides information on dates and cause(s) of death for all deceased residents 1961–2003.[21] Using these two registers, it is possible not only to track the vital status of a given individual but also to sample matched controls from the general population.

Inpatient Register This is an administrative database extensively used for medical research.[22] With a near complete coverage, information on every discharge from inpatient care has been stored since 1964 (the coverage became nationwide in 1987). For each discharge, information on discharge diagnoses and surgical procedures are coded according to the International Classification of Diseases (ICD). General and specific validation surveys suggest that almost 90% of the registered diagnoses are indeed correct when compared with the medical files.[22] Limitations of this register include lack of information on the grounds for each registered diagnosis, absence of information on treatment, and limited information about when symptoms started, or date of diagnosis of chronic diseases.

Swedish Cancer Register This provides individual based data on cancer occurrence since 1960, currently updated through 2004.[23] The high reporting rate of diagnosed malignancies is maintained through double and mandatory reporting by both clinicians and pathologists. Although the registry itself does not store biological specimens, methods are available for retrieval and reanalysis of such specimens.

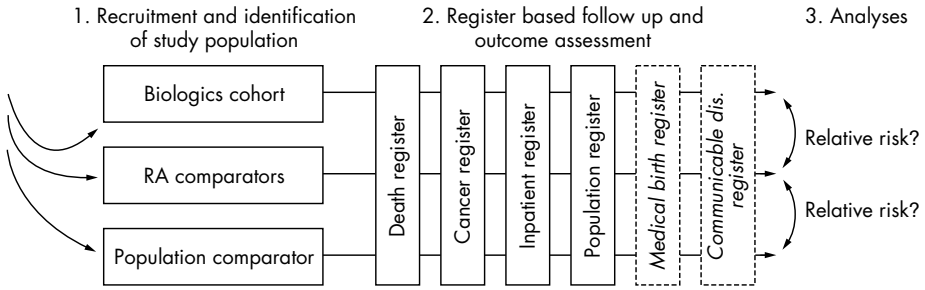

Figure 2 Principle for register linkages using Swedish biologics cohorts, comparator cohorts, and national registers.

Register linkages

The national registration number is a 10 digit number assigned to all Swedish residents alive in 1947 or born thereafter.[24] Because this number is recorded in all medical files, in all RA registers, and in all nationwide health and census registers, record linkage of these prospectively recorded data sources can be performed. For the scientific studies based on register linkages of ARTIS, annual register linkages have been performed at the National Board of Health and Welfare and at Statistics Sweden. From these linkages, we have abstracted and compiled information for each study. Similarly, register linkages may be performed using the subset cohorts, such as the SSATG, for which a local comparator RA cohort has been used.[25]

Ethics and confidentiality

Access to individual pieces of information from ARTIS and from the Early Arthritis Register is restricted to the physician caring for the patient in question. Scientific studies using these registers are subject to scrutiny by the ethics review board.[26] To comply with current legislation, to avoid repeated (and in practice impossible) informed consent procedures for all 100 000 or so subjects who are covered by the linkages, and to maximise the integrity of each person's data, the process of register linkage includes irreversible de-identification of individual data. In practice, this means that after the linkage has been completed at the central agencies, the national registration number of each person is stripped and replaced by a random number. This number is still unique to each person and can thus be used to match information from different registers, but ensures that the true identity of each person is no longer known. In the event of a signal or need to perform a more detailed study such as a nested case-control study with scrutiny of medical files and review of biological specimens, a new application to the ethics review board is required.

Examples of safety issues examined by the Swedish biologics registers using register linkages

To examine the occurrence of malignant lymphomas in patients exposed to biological agents, regional as well as national Swedish biologics data have been used (linkage outlined in fig 2).

Through linkage of the regional SSATG register (757 patients, five lymphomas) to the Cancer Register, the incidence of malignant lymphomas 1999–2002 was compared with the lymphoma incidence in a community based comparator cohort of RA not offered biological agents (800 patients with RA from the largest city in the region, Malmö, two lymphomas 1997–2002).[25 27] In this comparison, the relative risk (RR) of lymphoma in the TNF antagonist cohort was 5.0 (95% confidence interval (CI) 0.9 to 27), and unaffected by adjustment for the Health Assessment Questionnaire (HAQ).

In a register based study based on the ARTIS register (including the 757 regional patients above) the incidence of malignant lymphomas 1999–2003 (4160 subjects, nine lymphomas) was compared with that of the Early Arthritis cohort (3703 subjects, 11 lymphomas), and with that of the Inpatient Register RA cohort 1990–2003 (53 067 subjects, 319 lymphomas). In this comparison, the RR in the ARTIS cohort was 1.1 (95% CI 0.6 to 2.1).[28]

Although the apparent discrepancy between these overlapping assessments may appear confusing, it is important to keep in mind some of the differences between the assessments, differences that also point to general factors that are important for *any* evaluation of observational cohort studies like those from drug registers. Firstly, statistical precision was low in the first assessment, and only moderate in the second. Secondly, the lymphoma risks in three *comparator* cohorts were different. Indeed, when the comparators were in turn compared with the general population, the lymphoma risk in the comparator used for SSATG was lower (RR = 1.3) than in the national RA comparator cohorts (RR = 1.7 and 1.9, respectively). Thirdly, the biologics cohorts used reflected somewhat different patient selections. The SSATG analysis was by 1 year the first performed and thus largely included patients starting TNF antagonist treatment in the early years (1999–2001) with somewhat longer mean disease duration than in the national assessment, which included a larger proportion of subjects starting TNF antagonist treatment in 2002 and 2003.

Using similar follow up designs, a series of risk assessments for malignancies,[28 29] infections,[30] and cardiovascular disease[31] have been performed, both regionally[25 31] and nationally.[28–30] Importantly, the same register linkages have not only permitted a comparison of biologics-naïve and biologics-exposed RA cohorts, but also a comparison of biologics-naïve RA cohorts with the general population. For instance, in the absence of TNF antagonists, RA is associated with an increased occurrence of tuberculosis.[30]

Examples of other clinical issues examined by the Swedish biologics registers

The main argument for a national approach to biologics registration in Sweden is that several of the purported adverse effects of biological agents have such a low incidence that only a national effort may gain sufficient statistical power. The main argument for the regional initiatives is that they may contain more detailed data on treated patients. They may therefore be better suited for assessments of, for example, clinical hypotheses related to effectiveness, which may require a smaller number of exposed subjects but better resolution of response to treatment than can be gathered from the national data. For instance, the SSATG register has reported on health economic data,[32] and on how response criteria perform in clinical practice.[33] Analyses of data from the STURE register have examined the benefits of switching

between biological agents,[34] and on dose and frequency escalations with infliximab.[35]

DRUG REGISTERS, DO THEY HAVE A FUTURE?

In our view, systematic safety surveillance and collection of efficacy data using systems like ours, whether local, regional, or national, have come to stay. Indeed, we believe that they will evolve into an integral part of the drug approval process. With respect to the safety of TNF antagonists, the preliminary reports on infections, cancer, and lymphomas only mark the end of the beginning of follow up of exposed patients. Indeed, a comprehensive assessment of long term modifications of lymphoma risks, for instance, will require substantially more person-years of follow up, and more data than presently available for adjustment and stratification on accrued and present disease activity.

We advocate the use of systems like ours as part of everyday evidence based medicine in the age of electronic medical record keeping. They require efficient reporting and feedback mechanisms so that reporting involves a *minimum* of extra work, but provides a *maximum* of useful quality assured, real time information for the clinician, during the patient's visit. In this respect, we think that our approach stands a high chance of surviving beyond the first years of follow up of the recently introduced TNF antagonists.

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