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# The CORRONA Database

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## ABSTRACT

**Background.** *Large, long-term data bases are needed in order to provide information on the safety and efficacy of new agents used in the treatment of rheumatoid arthritis (RA) and psoriatic arthritis (PsA). These databases can provide data which is well beyond what is available from industry-sponsored investigations.*

**Methods.** *The structure, governance, content, context and developmental plan of the CORRONA database is described.*

**Results.** *The CORRONA database has grown from start up in 2002 to the largest independent database in North America which collects data from both rheumatologists and patients at the time of a clinical encounter. Data are collected as often as every 3 months in RA and every 6 months in PsA. As of the time of this writing, the CORRONA database consists of approximately 9,000 patients with RA and 1,000 with PsA. Data can be used to elucidate toxicities found in frequencies which would be considerably less common than can be uncovered in industry-sponsored investigations. In addition, actual prescribing patterns and responses in clinical practice can be investigated and described.*

**Conclusion.** *After 3 years of data collection, the CORRONA database is now appropriately able to make significant contributions to our understanding of the safety, efficacy of drugs, as well as demographic, and socioeconomic profiles of patients with RA and PsA. It has evolved from a nascent database to a mature one poised to make significant contributions.*

## Introduction

The Consortium of Rheumatology Researchers of North America (CORRONA) was founded by a group of academic rheumatologists and began collecting data in 2002. CORRONA was designed to fill a void in North America as, at the time of its founding, there was

no database independent of the pharmaceutical industry which collected data in the clinic from both rheumatologists and patients.

There was also a perceived need to develop a database which collected clinical information from all patients in a practice with rheumatoid arthritis. With the introduction of expensive new therapeutic agents, it was apparent that longitudinal, long-term, 'real world' data would serve the rheumatology community well. There was also the perception that busy physicians would welcome a system which enabled them to treat individuals with chronic diseases associated with complex comorbidities in a smart and efficient manner while reliably tracking standard outcomes, laboratory and imaging data as well as toxicities. The new agents have the potential for great individual and societal good, as well as the potential for frightening toxicities. It was apparent that reliance on voluntary reporting from post-marketing surveillance to the Food and Drug Administration (FDA), and various long-term phase IV studies would not be adequate to fully inform rheumatologists and patients about outcomes in this evolving clinical marketplace.

## Description of the database

At the time of this writing in June 2005, CORRONA has a database consisting of 8,755 patients with rheumatoid arthritis (RA), 955 patients with psoriatic arthritis (PsA), and approximately 1,000 patients with a primary diagnosis of either osteoarthritis or osteoporosis. A total of 83 sites are scattered throughout 33 states in the United States (see site map, Fig. 1). A total of 200 rheumatologists now participate. Patients with RA or PsA are enrolled at the time of a routine visit at a site. Patients are then followed as often as every 3 months for RA, and every 6 months for PsA, OA, and osteoporosis (OP). At the time of this writing the database consists of more than 30,000 total vis-

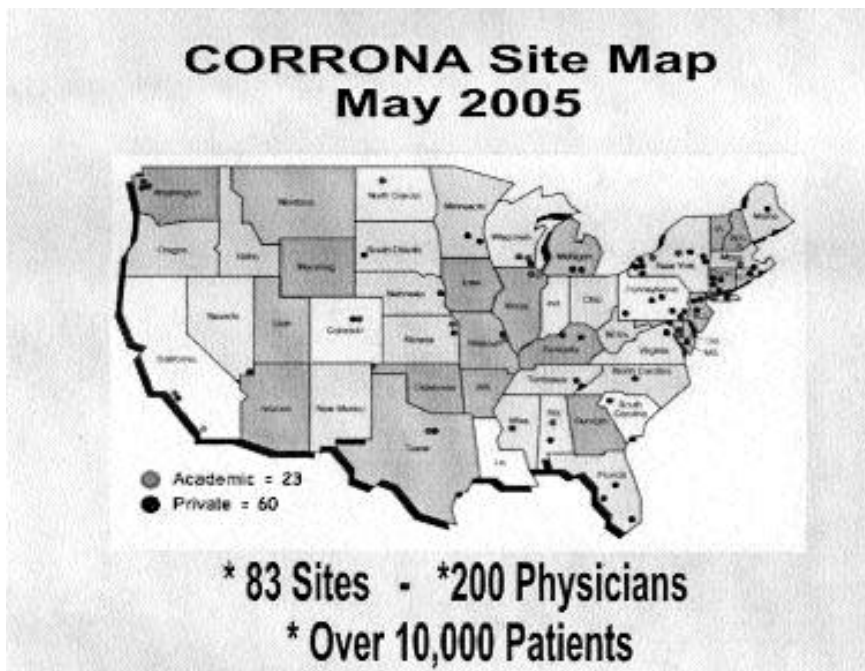


Fig. 1.

its, with a mean duration of follow-up of 1.27 years. The mean time between follow-up visits for patients in the database is 5.7 months, with a total of 7368 patient years for patients with rheumatoid arthritis.

#### Academic reports

In order for a longitudinal database to be of value, it must mature to the point that data are meaningful. That is, the data have to have intrinsic recognizable value. This 'tipping point' occurs when there are enough patients in the database for a sufficient length of time to enrich the data to the point of relevance for the rheumatology community. Getting to the point of meaningful data is obviously a process which does not occur overnight. At the end of our third year of existence, we can now say with some confidence that CORRONA has reached that point. Earlier observations from the database published in abstract form (1-9) have recently been followed by full-length reports (10) and several other data submissions to both the annual meeting of The European League Against Rheumatism (EULAR) (11-15) and the annual meeting of the American College of Rheumatology (16-27). It is apparent that the data have now been enriched and have matured to

the point of clinical relevance. It is appropriate then that a flurry of reports begin to emerge at this time.

#### Context

It is perhaps somewhat surprising that similar efforts have not been previously initiated. Others have advocated the collection of data in the clinic using standardized forms for many years (28, 29). In addition, standardized longitudinal databases have emerged in Sweden (30) and the United Kingdom (31) and these have already made substantial contributions. The Swedish data are derived from a National Health Care Registry, so that the data comes from a pre-existing computer system established by the national health care delivery system of that country. The system in the United Kingdom is voluntary and not universal.

It was not clear whether busy rheumatologists in the United States would voluntarily participate in data collection in the clinic. These physicians were felt to be too "flat-out busy" to voluntarily assume the added task of collecting data on forms. Thus, any system which was based on the assumption that physicians would collect data had to have considerable built-in advantages or incentives for the clinician if it was going

to realistically be capable of moving busy practitioners to change the way they did things.

There were, however, several historical themes which have favorably affected the adoption of the process. Some of these factors were new and not previously available to favorably influence the widespread adoption of data collection. We will briefly summarize these themes and see how they influenced the climate at the time in which CORRONA was founded in the United States.

First, the electronic revolution of data collection and management in the late 1990s and early part of the first decade of the new millennium has changed the way in which we all view the collection of information. Physicians manage multiple, complicated issues including disease states, drugs with toxicities and human beings with all their complexities. The number of variables associated with effectively managing these disparate data elements was and is large indeed. It makes a great deal of sense to have computer help in this complex process. Fortunately, clinicians who are considering adopting the process now have established models outside of our discipline for information management, as most are familiar with the advantages of computers by now.

It is in fact unimaginable that a group of professionals with years of post-graduate training would not already rely on computer software to help them with the tasks of providing quality patient care while tracking the many complexities associated with the management of disease outcomes, toxicities and comorbidities. But, as has already been described, most practicing rheumatologists in the US completed their training at a time when computers and databases were not a part of their learning experience. These individuals became accustomed to making clinical decisions from their considerable fund of established medical judgment, or gestalt, developed over the course of years of practice.

It was frankly difficult to recognize that there could have been "a better way" to take care of patients. Many physicians still cannot acknowledge that a better

and more efficient pathway exists. Yet it is readily apparent that the benefits would be great if an array of clinical information were available to the treating rheumatologist at the time of every clinical encounter. This, combined with the increased awareness that even the most careful of physicians will inevitably omit a critical process when it has to be repeated hundreds or thousands of times, makes the inclusion of an efficient and standardized patient interaction process critical in order to avoid errors of omission.

Second, there is a need for documentation to assure that appropriate procedures have been performed in order to bill at a certain level of complexity. In the US, certain elements of the clinical encounter such as two vital signs, a patient social history as well as certain critical elements of the rheumatologic examination such as a joint count, have to be present in order to defensibly bill Medicare (the US government sponsored system for payment of medical expenses for individuals over the age of 65) for what is called a "level IV" encounter. In the absence of a standardized system for assuring the presence of all of the necessary elements required to bill at this level, practice income suffers. The CORRONA forms provide the necessary documentation for this increased level of billing.

Third, busy clinicians need help in simply getting through their day. The complexities of patient care and appropriate documentation in the present highly demanding political, economic and social climate in the US have combined to create increased stress for all physicians, including rheumatologists. A system which provides a focus for a clinical encounter, which is time neutral, and provides patient care and documentation benefits as described does lessen stress. A busy rheumatologist can complete an encounter knowing that all of the critical elements of care have been addressed and that documentation has been provided. This assurance actually lessens stress while providing increased job satisfaction. This element of the data collection process should not be underestimated.

Fourth, rheumatologists utilizing COR-

RONA can access data on the web on all of their patients. By using their unique sign-on code, a participating clinician can view clinical, laboratory and demographic data on the web. Customized analyses of individual patient data, patients grouped in a variety of ways (i.e., by physician or provider, gender, age, drug prescribed, insurance type, laboratory abnormality, radiographic status, bone density status, etc.) is possible. This additional element of the database gives clinicians at each site an unprecedented analytic tool which actually goes beyond what is possible with an electronic database. E-databases are able to provide descriptive data on many elements of disease and this feature is of course also found in the CORRONA database. However, e-databases are not able to create customized cross analyses that combine various data elements and present them in a customized graphic format. This additional element, which is provided by the CORRONADatabase, allows a level of sophisticated learning and appreciation of the nature of practice patterns that has no precedent. It can be used for business reasons: patients on drug A do better than patients not exposed to it; disability, hospitalizations and orthopedic procedures are diminished when we treat in this manner as documented in our database, etc. The information can therefore be used to defend prescribing patterns of expensive medications, maintaining therapeutic options with local payers.

The information can also be used for academic investigations: Does the combination of drug B used with methotrexate result in better outcomes than drug C used with methotrexate? They can be used to compare practice performance and outcome measures amongst several rheumatologists within the same practice in order to determine who is performing in a manner which actually results in the best practice and patient outcomes. Several parameters could be used for this analysis including joint counts, MHAQs, frequency of corticosteroid injections, laboratory parameters, hospitalizations, orthopedic procedures, development of comorbidities, etc.

Fifth, rheumatologists are paid by CORRONA for completing both baseline and follow-up forms. This payment can represent a significant additional source of income at a time when other revenues are diminishing.

Sixth, many clinicians feel only partially fulfilled by the process of seeing patients. Participation in CORRONA allows rheumatologists the opportunity to contribute to the greater good by participating in a national team effort led by academicians within their own discipline whom they respect, and to learn more about the diseases which they treat. In addition, individual site participants have the opportunity to query the entire database annually by submitting questions to the Scientific Committee of CORRONA. These submissions are reviewed in a timely manner prior to the deadline for the submission of abstracts to the annual meeting of The American College of Rheumatology. They are numerically ranked by our scientific committee for quality and, if accepted, any member of the network can utilize the services of the full-time statistical support staff of CORRONA in order to develop the data for a submission and manuscript. All of these components of context favoring the adoption of a web-based database are summarized in Table I.

### Governance

CORRONA is run by a board of directors of rheumatologists. Its governance is entirely independent of any outside industry influence. The board meets monthly in a teleconference to discuss all issues of governance. Scientific pol-

**Table I.** Historical and contextual reasons favoring widespread adoption of the CORRONADatabase.

1. Information management
2. Documentation for billing
3. Stress reduction from knowing that all elements of an encounter have been efficiently covered
4. Ability to perform customized analyses on data from an individual site
5. Payment for baseline and follow-up forms
6. Participation in the academic activities of the network

icy is set by the Scientific Committee of six members which also determines the merits of abstract submissions and fellowship awards. An Executive Committee of five members develops policy recommendations which are then brought to a vote by the entire board membership at the time of the monthly meeting. A recruitment and follow-up committee develops policy to help rheumatologists at sites and disseminate information to CORRONA patient participants regarding the accomplishments of the database and the organization.

Board governance is based upon the principal of "one man, one vote". That is, all opinions, votes and input count equally, without any single individual having more 'pull' than anyone else.

Board membership is for a finite period and new members rotate on while others rotate off. Physician members at CORRONA sites are eligible to be nominated for participation on the board. Individuals are chosen on the basis of their track record of academic leadership, contributions to the rheumatology community, and their potential for other organizational contributions because of demonstrated commitment to our goals, or unique skills which can contribute to the overall success of the organization. At all times a philosophy of inclusion in the process is adhered to by members of the board of directors. The governance of CORRONA does not wish to be perceived as an "old boys club" of privileged insiders. A member of the board is judged annually on his or her tangible contributions, empowering so-called 'less visible' members to achieve positions of influence simply by hard work.

### Funding

CORRONA derives operating funds from the pharmaceutical industry (a group of contributors whom CORRONA refers to *en bloc* as "Pharma"). Pharma purchases the ability to access data from the CORRONA database. However, Pharma is not allowed to simply see or use raw data. Rather, the company purchases a number of hours of access quarterly to the CORRONA biostatistical team. Pharma submits a

query for analysis of a particular question, or questions. In the next step, a member of the CORRONA Board of Directors sees the query(ies) and determines if they are appropriate. That is, is the database able to address the question and is it an appropriate question? (The possibility of Pharma to ask questions which identify competitors by name is limited [see below].)

Assuming that the answers to all of these questions are affirmative, CORRONA's fulltime biostatistical staff begins a process of back-and-forth communication with the individuals in Pharma who have submitted the query. Analyses are then submitted and refined in an iterative process until all of the elements and components of the submission are answered in a satisfactory manner. It is through this support from multiple pharmaceutical companies that CORRONA has derived working capital which could then be used to provide legal, biostatistical, infrastructure and IT support, while paying rheumatologists for completing the forms.

### Rules for utilization of CORRONA data by Pharma

The pharmaceutical industry is limited in the use of CORRONA data since individually named, patent-protected, competitor products cannot be identified in a promotional package or publication. Pharma can however compare their product with grouped products. That is, anti-TNF product "A" can compare results with products "B" and "C" grouped together, and not individually identified. Of course, all drugs can be compared with any generic agent, or group of agents in any manner. Generic agents can be grouped together with patent-protected drugs.

It was felt that the above policy protected CORRONA from the potential for inappropriate use of its data in marketing battles between companies. Inevitably, it was felt that the credibility and stature of the database could be compromised if it were used primarily for marketing purposes.

In addition, before submitting any CORRONA-derived report in the public domain, Pharma partners have to submit the report to the CORRONA

biostatistical team for review. Thus, there are two quality control steps which Pharma must perform. First, they receive answers to their submitted query from our own biostatistician without seeing the raw data. Second, before 'going public' with a report, the data must again be reviewed by the CORRONA biostatistical team and checked for statistical veracity and accuracy. Finally, a member of the CORRONA board of directors may serve as an author on any submitted academic report or publication. (This process is not mandatory, but is generally regarded as a "plus" by industry.) In this manner CORRONA provides additional quality oversight on the manner in which our data are reported to the rheumatology community.

### Future directions

#### Pharmacogenomics

CORRONA is in an ideal position to serve as the database for which pharmacogenomic data on the rheumatic diseases is derived. This is because the data are not limited to either a single drug, or even a single disease state. The CORRONA database has already begun to examine the association between certain single nucleotide polymorphisms (SNPs) and disease outcomes from our database (16-18), and we anticipate greatly expanding these analyses with the addition of proteomic and biomarker measures.

One of the major developments in medicine in the last several years has been the completion of the identification of human genes in the Human Genome Project. While many associations with rheumatic disease in general, and rheumatoid arthritis in particular, have been identified, the science is not yet at the point where these analyses can support clinical decisions regarding treatment for patients. It is likely that thousands of patients will need to be studied in order to draw reliable conclusions. The marriage of a large longitudinal database such as CORRONA with the ability to test SNPs, proteomics and biomarkers will provide an unprecedented opportunity to derive these data as new and existing agents enter the clinic.

### Quality management

Physicians in the US are becoming increasingly aware of the need for the measurement of outcomes. An outcome which can be measured and assigned a numeric value can be tracked and has significant potential intrinsic value. Fortunately, validated outcome measures have already been developed and disseminated for widespread use in clinical practice. Thus "ACR20, 50 and 70" measures are routinely quoted by knowledgeable rheumatologists who are familiar with the published literature regarding the use of new agents. These outcomes can in fact be calculated from the CORRONA database as it contains all of the elements needed to calculate the ACR scores. However, it is becoming widely recognized that ACR outcome measures are inadequate to represent change in individual patients. This is because these outcomes are binary systems in which an individual is categorized as achieving, or not achieving, the ACR outcome of interest. As such, they miss a gradation of responses which are in fact captured by the DAS44 and DAS28 outcome measures. Statistically, the ACR outcome is treated as a categorical variable, while the DAS is a continuous variable.

The above consideration is offered in the way of background, as it is likely that a validated outcome measure such as the DAS28 will be used as a standardized, validated, continuous variable which can be used to track the clinical effectiveness of new and expensive interventions. Aside from the need to provide documentation for billing, and better patient-related services, utilization of the DAS28 from the elements of the CORRONA database will provide one of the key components of measurement (as performed by the physician, or physician extender, a continuous numeric value can be assigned) to track patient progress.

Some may say that it is not necessary and it is unlikely to be required that rheumatologists perform measurements like the DAS. They may be correct now, but in the brave new world of quality assessment and the assignment of monetary rewards for quality (32), it is apparent that objective, defensible

measures of outcome (such as the DAS28; the MHAQ, which also provides a numeric value that can be tracked; and the utilization of an electronic system that enables the clinician to track and monitor a variety of toxicities and comorbidities, receive prompts about needed elements such as TB skin testing, and the testing and re-testing of bone density) will be necessary in order to fulfill the "QC" bill. Indeed, plans are now in place for Medicare to reward physicians with such quality measures by 2006 (32, 33).

### Sponsored studies

One of the original stated goals of CORRONA was to organize and sponsor its own studies of interventions for rheumatic diseases. There is at present no reliable mechanism to sponsor a study of an intervention of a new combination of existing agents to treat patients with either RA or PsA. The rheumatology community and patients with rheumatic disease share clinical research choices which are understandably limited to those of the Pharma industry. This is because Pharma is the primary sponsor of clinical research in our discipline. Although funds for clinical research are theoretically available from the National Institute of Health (NIH) and the Arthritis Foundation, in practice the former has not funded much in the way of clinical research and the latter does not have the funds for large-scale investigations.

There is thus the need for an independent entity to develop the funding and infrastructure necessary to investigate the potential for combinations of new and existing agents to be used together. Other disciplines such as oncology have for some time been using protocols designed by experienced clinicians to determine which combination of drugs works best. It is possible that the new/biologic agents combined with methotrexate are not an ideal combination if the therapeutic goal is to place patients in remission. If patent-protected drugs are to be prescribed and used together in rheumatology with the goal of achieving a safe and lasting remission, a mechanism for funding investigations that is independent of Pharma

will have to be developed. It is the hope of the board of directors that CORRONA can supply this mechanism.

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