

Title:

A Medical Informatics Grand Challenge: the EMR and Post-Marketing Drug Surveillance

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Abstract

A grand challenge is a fundamental problem whose solution requires significant increases in scientific knowledge and technical capabilities. Drug post-marketing surveillance, the early detection of unexpected adverse side effects caused by newly available drugs, is a significant issue of great social and economic import. Such activities are currently inadequately performed due to significant technical, scientific, industry and societal difficulties, and this has harmed patients and the pharmaceutical industry, an important component of the healthcare system and the economy. Utilizing the emerging national EMR to improve drug post-marketing surveillance is an approachable medical informatics grand challenge with significant potential benefit to multiple stakeholders including patients, the pharmaceutical industry, healthcare payers and government. This paper discusses the difficulties, challenges and possibilities for joint industry-academic medical informatics collaborations in this domain.

Keywords

Drug Industry

Product Surveillance, Postmarketing

Drug Safety

Drug Toxicity

Adverse effects (qualifier)

Adverse Drug Reaction Reporting Systems

United States Food and Drug Administration

Medical Records

Medical Informatics

Introduction

A *grand challenge* is a fundamental scientific or technologic problem whose solution requires significant increases in current levels of scientific knowledge and/or technical capabilities. Solutions should improve the health of the population and be achievable in a decade¹. An approachable grand challenge in Medical Informatics, of great benefit to the health of the population and of current high visibility, is leveraging the developing national electronic medical record (EMR) and healthcare IT infrastructure for pharmaceutical post-marketing surveillance; that is, improving early detection of drugs released to market that cause unforeseen, unwanted harmful side effects (adverse drug events or AE's).

In 2004 the U.S. government announced support for development and implementation of a nationwide, interoperable health information technology infrastructure to improve the quality and efficiency of health care². In the same year, several high-profile drug safety cases raised concerns about the ability of the Food and Drug Administration (FDA) to manage issues raised by adverse drug events³. These drug safety cases have had significant legal, financial and reputational repercussions upon the pharmaceutical industry, a major worldwide industry of great importance to public health and the economy. At the intersection of these two issues there exist compelling synergies for improvement of drug and patient safety.

In its 2007 report “The Future of Drug Safety: Promoting and Protecting the Health of the Public”, the Committee on the Assessment of the US Drug Safety System of the Institute of Medicine has written that:

Informatics experts should track progress on the national health-information infrastructure, look for opportunities to gather information about drug safety and efficacy after approval, coordinate partnerships with external groups to study the use of electronic health records for [drug] adverse event surveillance, participate in FDA's already strong role in setting national standards and track the development of tools for data analysis in industry and academe, and encourage the incorporation of the tools into FDA practice where appropriate⁴.

These recommendations come at an opportune time for EMR and medical informaticists, whose cross-training, as per the NIH observation about informationists, provides a unique perspective on the acquisition, synthesis and application of information to problem solving in clinical and biomedical domains⁵.

A systematic review of healthcare information technology's impact on quality, efficiency and costs of medical care was conducted during 2003-2005, requested and supported in part by the Agency for Healthcare Research and Quality of the US Department of Health & Human Services (HHS). This study concluded that while several exceptional "benchmark" institutions have demonstrated the efficacy of health information technologies such the electronic medical record (EMR) in improving quality and efficiency, the likelihood that other institutions could achieve similar results remained unclear. The impact of the technology on healthcare costs was also unclear⁶. Further, in a recent analysis based on technology diffusion theory, the EMR is predicted not to become ubiquitous to all providers including small private practices until at least 2024⁷. At this juncture in the long history of healthcare information technology^{8,9}, a history

marked by much innovation and promise but also “growing pains”, implementation difficulties, and even adverse outcomes^{10, 11, 12, 13}, these are not the most encouraging findings for promoting widespread EMR investment and adoption.

If the transition from paper to EMR is to be completed in a more timely fashion, other avenues to encourage the necessary, significant investments and efforts needed may be beneficial. It is reasonable to believe that leveraging new, innovative capabilities made possible by widespread, interoperable EMR and related clinical IT will increase enthusiasm and the societal pace of adoption. This is especially true if the innovations are readily recognized as valuable to all stakeholders including individuals, regulators, payers, and the broad healthcare industry. Drug safety surveillance offers these possibilities.

Turbulence in a critical healthcare industry

Reports of unexpected drug adverse side effects, including fatalities, have unfortunately become a familiar feature in the literature and media in recent years. As an example, a story on Feb. 15, 2006 about AstraZenica’s anticoagulant drug Exanta reports it withdrawn from the market due to episodes of severe liver damage¹⁴. This phenomenon is an issue of national importance affecting the well being of companies that comprise a significant part of the U.S. economy, one (Merck) being a component of the Dow Jones Industrial Average¹⁵.

Merck was accused of ignoring or concealing adverse events data from its own early, relatively small clinical trials on anti-inflammatory pain medicine VIOXX, as well as ignoring secondary

data coming from other sources such as a retrospective study based on records of 1.4 million members of Kaiser Permanente, the largest U.S. nonprofit insurer. The company said these studies were not statistically valid to prove cause and effect for VIOXX-related cardiovascular events¹⁶. However, the company withdrew VIOXX from the market when a later, somewhat larger clinical trial of its own appeared to show a small but definite increased incidence of serious cardiac side effects compared to other non-steroidal anti-inflammatory drugs.

Outspoken critics on drug safety issues such as Dr. David Graham, a senior official in the FDA's Office of Drug Safety often come under fire for their views: "A Food and Drug Administration official [Graham] who sought to estimate the harm done to patients by side effects of the painkiller Vioxx said yesterday that his supervisors tried to suppress his conclusions, according to Sen. Charles Grassley (R-Iowa)"¹⁷. Since 1988, Graham has called for the removal of 12 drugs from pharmacy shelves, leading to 10 actual recalls of harmful drugs. Graham told Congress that FDA's problems with ensuring drug safety were "immense in scope" and left the nation "virtually defenseless" against the chance that unsafe drugs will reach consumers¹⁸.

Drugs can have adverse events that are both unexpected and opposite in effect. Gatifloxacin, an antibiotic, has been found to cause a substantial increase in the risk of emergency room visits for hypoglycemia (low blood sugar) in outpatients compared to other comparable antibiotics. In a second study, patients receiving gatifloxacin had more than 16 times as high a risk of hyperglycemia (high blood sugar) as did patients receiving other comparable drugs. Some of these rare events were life-threatening. It was noted that the time from approval of this drug in 1999 to changes in the drug labeling took six years. It was felt that a comprehensive plan to

“respond appropriately and expeditiously to signals indicating potential drug-safety problems”
was essential in order to reduce unnecessary adverse event-caused morbidity and mortality¹⁹.

Exploratory Studies of EMR for Drug Surveillance

Use of EMR for drug surveillance is not merely a hypothetical capability. There have been exploratory studies on this topic and related areas.

As examples, Murff et al reviewed current methodologies for detection of clinical adverse events including electronic methods that can detect events using coded data, free-text clinical narratives, or a combination of techniques ²⁰.

Gandhi et al conducted a similar review specifically aligned to drug safety issues and believe computerized monitoring for adverse drug events using rules or “triggers” is a high yield and relatively inexpensive strategy that should be adopted by healthcare organizations ²¹.

Nebeker et al described prospective daily reviews of EMR data performed by pharmacists as an effective way to detect adverse drug events ²².

Honigman et al reported on an automated, computer-based retrospective analysis for adverse drug events of one year of data from an EMR, including records on over 23,000 patients. The conclusion was that computerized search programs can detect adverse drug events in such data and that such detection programs demonstrate “value added” for the EMR ²³.

Hegmann et al described a system to detect possible bioterrorist attacks during the 2002 Olympic Games using an EMR-based bioterrorism surveillance system. The system implemented 50 different analyses that examine a range of symptoms to detect and track infectious diseases ²⁴.

Research has been done specifically in the application of data mining techniques in drug surveillance. Wilson describes knowledge discovery in databases (KDD), a technique to detect potential adverse drug events involving the selection of data variables and databases, data preprocessing, data mining and data interpretation and utilization. They describe data mining as encompassing a number of statistical techniques including cluster analysis, link analysis, deviation detection and disproportionality assessment which can be utilized to determine the presence of and to assess the strength of adverse drug event signals. The authors concluded that in view of the importance of adverse drug events and the development of massive data storage systems and powerful computer systems, the use of data mining techniques in knowledge discovery in medical databases is likely to be of increasing importance in the process of drug surveillance as they are likely to be able to detect signals earlier than more common methods currently in use ²⁵.

Efforts in using EMR's for drug post-marketing surveillance can also serve as a test bed for identifying and resolving issues in broader uses of national EMR of even greater significance than drug surveillance, such as syndromic surveillance for early epidemic detection or detection of chemical terrorism or bioterrorism. Syndromic surveillance refers to using health-related data that precede diagnosis and signal a sufficient probability of a case or an outbreak to warrant further public health response ²⁶.

These exploratory studies hold promise towards leveraging the EMR to facilitate solution of pressing, seemingly intractable problems in drug safety surveillance.

Deficiencies in existing drug surveillance mechanisms

Pre-marketing drug evaluation processes are still largely based on formal, extremely expensive randomized clinical trials and manual information collection processes that cover a relatively small sample of patients. Most drug-development programs designed for treatments of symptomatic indications are underpowered to detect any increased risk of rare drug reactions or change in background event rates attributable to the drug²⁷. Clinical trials typically involve several thousand subjects, and they pick up common problems--affecting 1 person in 500 or 1 in 1,000 - reasonably well. They aren't designed, however, to pick up rare adverse events, for example, occurring at a rate of 1 per 50,000 exposures. Unfortunately, when a drug is released and used by millions a 1 per 50,000 adverse event rate can result in a significant absolute number of morbidity and mortality cases, causing significant public clamor, liability and reputational damage to the involved pharmaceutical company.

The existing systems of post-marketing drug surveillance are largely inadequate as well. Most post-market studies funded by industry are intended specifically to expand the market for a drug, and such studies are usually not undertaken unless the calculated probabilities indicate that the study will yield a positive financial return²⁸. Avorn observed that it is naive to expect companies to voluntarily fund studies that could sink lucrative products²⁹. In approving a new

drug, FDA may demand that a company conduct additional safety trials after release to the public, but the agency can't enforce these post-approval studies, which are tedious and expensive, as FDA has "limited authority to require that sponsors conduct post-market safety studies"³⁰. More than half of those agreed to by manufacturers never occur, according to a Department of Health and Human Services report in the March 15, 2004 Federal Register³¹.

Even when performed, there are ongoing issues with post-market drug studies:

The [FDA's first annual Federal Register (FR) report on [drug] postmarketing studies] defines the status of 1,339 open manufacturers and 223 open postmarketing study commitments for biological products by 44 manufacturers. Of the open postmarketing drug studies, 820 (61%) are yet to be initiated; 285 (21%) are ongoing; 25 (2%) are delayed; 8 (1%) have been terminated before completion but the manufacturers have not submitted a final study report; and 201 (15%) have been either completed or terminated, and the FDA has received the final study report. Also in the drug area, annual reports for 289 (22%) of the open postmarketing commitments are overdue³².

Other existing post-marketing surveillance programs have significant deficiencies, such as the FDA MedWatch adverse events reporting program via forms 3500 and 3500A³³. Such systems, being ad-hoc, fail to produce any data at all if the practitioner does not realize a problem may be due to a drug - and this is likely the situation in a majority of cases. FDA MedWatch is also lacking in standards and controlled terminologies, and as such are subject to the whims and biases of individual clinicians and the "blurred data" that generates. This "mainstay" of drug

safety thus suffers from underreporting, variable data quality as well as a lack of a mechanism to assess confounding risk factors. The lack of systemic collection and analysis of post-marketing data on the use of drugs and the outcomes of treatment has delayed the discovery of some serious problems until millions of people have been exposed³⁴. "Simply looking for heart attacks and strokes in individuals taking the drugs isn't enough," according to Alastair Wood, chair of pharmacology at Vanderbilt University³⁵. "Sometimes, a drug triggers such an unusual problem that it's fairly easy to connect the dots," Wood says. "But there was no possibility that you could discern a heart attack due to Vioxx from a heart attack not due to Vioxx."

According to the Wall Street Journal, the FDA is moving to improve how it finds and responds to risks from medical products, including trying to do better "data-mining" of adverse events, that is, application of automated computer algorithms to detect patterns in data not apparent to the human observer³⁶. These are preparatory steps in the right direction. Due to dependence, however, on fragmented, non-standardized clinical data often of a financial/administrative rather than clinical nature and origin, and adverse events reports representing only a small fraction of the likely actual drug-caused events, such efforts might be described as "informational alchemy", akin to efforts in medieval times to turn lead into gold.

It has also been proposed that Medicare data, available on more than 40 million people, might create a data resource via linking information on drug dispensing to patients' other health information such as diagnosis and procedure claims. CMS has been moving towards integrating new drug claims data from Medicare Part D with the medical data from Medicare Parts A and B to help support FDA's postmarketing activities and CMS's goal of providing evidence on drugs

and drug use for a broad range of conditions³⁷. There are important limitations to these data as well. They may be skewed towards maximizing reimbursement. They do not identify some conditions with sufficient specificity, contain no information on actual drug ingestion, lack important information such as smoking status and body-mass index, often lack historical information, and include only drugs covered by health plans³⁸.

Other suggestions regarding additional drug safety oversight committees within or outside of existing regulatory agencies amount to no more than incremental change, since the basic inputs (i.e., data) to such committees will not have been improved upon. For example, a new FDA Drug Safety Oversight Board will not increase the ability of the agency to remove unsafe prescription drugs from the market and could impede efforts to make medications safer, according to FDA safety officer David Graham and Senate Finance Committee Chair Charles Grassley (R-Iowa). Graham criticized the structure of the board, which he called "severely biased in favor of industry," and said that "FDA cannot be trusted to protect the public or reform itself."³⁹

In a 2006 U.S. Government Accountability Office (GAO) report to Congress on drug safety requested after congressional hearings, a GAO investigation found that:

FDA lacks clear and effective processes for making decisions about, and providing management oversight of, postmarket safety issues. The process has been limited by a lack of clarity about how decisions are made and about organizational roles, insufficient oversight by management, and data constraints ... There are weaknesses in the different

*types of data available to FDA, and FDA lacks authority to require certain studies and has resource limitations for obtaining data. Some of FDA's initiatives, such as the establishment of a Drug Safety Oversight Board, a draft policy on major postmarket decision making, and the identification of new data sources, may improve the postmarket safety decision-making process, but will not address all gaps ... FDA is taking steps to identify additional data sources, but data constraints remain*⁴⁰.

The report observes that while decisions about post-marketing drug safety such as labeling changes and warnings or market withdrawal are often based on actual adverse event reports, FDA cannot establish the true frequency of adverse events in the population with available data. The inability to calculate the true frequency makes it hard to establish the magnitude of a safety problem, and makes comparisons of risks across similar drugs difficult. Also lacking is systematic information on drug safety issues. A report as basic as a summary of the recommendations on safety actions made by the FDA Office of Drug Safety (ODS) cannot be generated because such information is not tracked⁴¹

The GAO report recommends, in essence, only refined policies, fine tuning of organizational charts and increased levels of authority for one department or office over another. No real scientific advances in post-marketing drug surveillance are posited. In fact, FDA itself has a history since the 1950's of founding committees and establishing and disestablishing multiple new research organizations (centers, bureaus and least one institute) to make major changes in the organization and management of its scientific endeavors. Most of these repetitive efforts failed⁴².

Leveraging growth of a national healthcare IT infrastructure

A post-marketing surveillance capability far surpassing the relatively unstructured systems that now exist is urgently needed to protect the public and prevent further damage to the pharmaceutical industry's reputation. Each day patients are treated in hospitals, clinics and medical offices, potentially useful information on short-term and long-term drug effects is generated. Unfortunately, most of this data either resides in unstructured medical charts, or is not recorded at all. Systems and methodologies are needed for capture of this everyday patient information in a structured and vigorous manner to enable comprehensive, detailed surveillance of drugs and devices as well as for broader societal purposes.

One possible solution to the data constraints faced by the industry and its regulators is leveraging the developing national EMR and healthcare IT infrastructure. It has been observed that the healthcare industry has significantly underinvested in information technology (IT) compared to other industries. In the U.S., less than one-third of hospital physicians and less than one fifth of physicians in private practice are using this technology, according to a CDC study using data from 2001-2003⁴³. A late 2006 systematic meta-analysis of studies from 1995-2005 by Jha et al at the Harvard School of Public Health showed that through 2005, only 24 percent of physicians used EMR's in the ambulatory setting, with solo practitioners, small practices, and safety-net providers less likely to use an EMR. Further, only 9 percent used EMR systems with functionalities such as electronic prescribing, and only 5 percent of hospitals used EMR-associated technologies such as computerized order entry⁴⁴.

A new Office of the National Coordinator for Health Information Technology (ONCHIT) in DHHS, founded by executive order of the Bush Administration in April 2004, has been charged with providing leadership for the development and nationwide implementation of an interoperable health information technology infrastructure to improve the quality and efficiency of health care and the ability of consumers to manage their care and safety⁴⁵. The cornerstone of these efforts is the Electronic Medical Record (EMR). This is a promising development.

Dr. David Brailer, first National Health Information Technology Coordinator at ONCHIT, called for efforts at employing the EMR for meaningful healthcare quality improvement, public health reporting, bioterrorism surveillance, quality monitoring, and advances in clinical trials.

However, there are no guidelines or broad experience in existence on how this is to be accomplished. Brailer indicates a major barrier is lack of system interoperability⁴⁶. This author would extend that to broad issues of information science, i.e., data quality, accuracy, reliability, as well as legal, regulatory and sociological issues. In fact, significant advances have been made messaging and controlled vocabulary standards^{47, 48}.

On the challenge of health data connectivity and sharing, Connecting for Health, a public-private collaborative of more than 100 organizations, has released a document entitled “Common Framework: Resources for Implementing Private and Secure Health Information Exchange.” The Common Framework provides the initial elements of a comprehensive approach for secure, authorized, and private health information sharing, so that patients and their authorized providers can have access to vital clinical data when and where they are needed. The Connecting for

Health Common Framework was tested in 2005 in Boston, Indianapolis, and Mendocino, Calif. The tests demonstrated that completely different health information networks can communicate with one another and exchange information, even if they operate on different technological platforms, use different registration systems, and organize patient data differently⁴⁹. Such efforts bode well for future interoperability in national health data initiatives as the nation's healthcare providers shift to EMR.

The pharmaceutical industry is itself starting to move beyond informal internal discussion of the capabilities a national EMR could bring. For example, in November 2005 a conference was held entitled "Merging Electronic Health Records & Electronic Data Capture: Integrating Patient Information with Drug Development" with presentations by numerous pharmaceutical executives and scientists, industry consultants, and technology companies:

We are forging ahead into a new era of electronic healthcare. The government's 10-year plan to automate healthcare information exchange by creating the National Healthcare Information Network presents an undeniable opportunity to synchronize patient information with drug development and increase the overall quality of patient care.

Drug & device companies have been struggling for years to successfully and efficiently move away from paper data collection towards electronic data capture and automated trials. Without a unifying body behind this push, data standards, interoperability and infrastructure compatibility have not been achieved. By piggy-backing on this government-lead initiative to automate healthcare, drug and device firms can reap the

benefits of the increased efficiency IT adoption at the hospital and physician level will offer and utilize this data for more streamlined drug development.

*ExL Pharma's Merging EHR & EDC Conference is the first opportunity for drug & device firms to gather with hospitals, physicians and vendors to discuss strategies for accelerating IT adoption and achieving cross-functional data interoperability to streamline processes, improve communication and maximize patient care*⁵⁰.

Talks related to EMR use in pharma were also presented at the Drug Information Association meeting in 2006⁵¹. Another DIA-sponsored conference in late 2006 focused on electronic clinical trials and facilitation by EMR⁵².

EMR systems will begin to provide detailed, comprehensive, increasingly standardized clinical information from the point of care on a patient base that in time will become orders of magnitude larger than in today's clinical trials. National registries in constrained healthcare domains such as invasive cardiology exist (the Genentech National Registry of Myocardial Infarction with data on data on more than 2.3 million cardiac patients collected since 1990 is an example). These registries are used today by medical centers and clinicians for new device and modality efficacy and adverse outcomes evaluation, identification of excessive complication rates, benchmarking, quality improvement, and other uses.

In a similar manner, the flow of well-defined clinical data from comprehensive EMR's could in theory be used for surveillance of drug complications as well as other epidemiological needs

such as syndromic surveillance for patterns suggesting infectious disease outbreaks, chemical and toxin exposure, and bioterrorism.

Since its transformation into a “wired” system in the 1990s, the VHA has developed a diabetes registry that holds detailed clinical data on 600,000 patients, which allows the system to track and manage higher-risk patients well enough to improve clinical outcomes by large orders of magnitude ⁵³.

The National Health System in the United Kingdom, which controls approximately 85 percent of healthcare delivery in the UK, will implement national portable electronic health records for the people of England through its National Programme for IT in the NHS ⁵⁴. The National Programme for IT is hoped to support in 10 years the approximately 60 million people of England that are projected to be served by the NHS at that time. The infrastructure will include new components integrated into existing national reporting databases:

- A centralized national database, called the NHS Care Record, to include all patient electronic health records. This data will likely be useful for epidemiological studies and drug surveillance on a national scale.
- A Patient Demographics Services operation that will act as an enterprise master patient index (EMPI) for the entire country, based on the patient's NHS number, a national patient identifier, and demographic and patient encounter information.

This same EMR technology can be leveraged to expand the clinical trials patient base itself and reduce the costs of paper-based clinical trials data collection where such trials are conducted, supplementing or replacing manual, proprietary methods currently employed.

Significant technical, scientific and social challenges

The EMR when more widely in use will have value in drug and other population surveillance, but the technical, scientific and social issues will be formidable in extracting meaningful information from the aggregate and acting upon those findings. Finding solutions to the scientific, organizational, legal, regulatory, industry and other matters that will arise will require significant cross-disciplinary research in medicine, medical informatics, statistics, information technology, information systems, public health, and other related domains.

Significant additional research and creative, flexible thinking will be required concerning the use of point-of-care data that may be less formally controlled than in a conventional randomized clinical trial. Faults in data quality and completeness are important issues. Stewart et al observe in use of enterprise EMR at Geisinger Health System in Pennsylvania that:

... the data needs of researchers, practitioners, and those who manage quality of care will create tensions that can best be balanced through protocols that both improve the completeness and standardization of data captured and reduce the cost of obtaining such data. Such technical solutions already exist in a number of areas and are used with increasing frequency at Geisinger. For example, we have begun to develop workflow and

data capture models for patient-completed questionnaires. Computerized order entry of prescriptions, tests, and procedures that require selection from a menu of predefined options can be set to require that one or more diagnostic codes be selected, indicating the intention behind the order. When used properly, predefined order sets, structured notes with defaults, and consultation templates standardize the content and organization of data input and can even enable structured, codified data capture. Even these rudimentary EHR protocols have the potential to contribute meaningful evidence that will complement knowledge gained from randomized trials ⁵⁵.

Platt observes that the impending availability of vast electronic health information databases has raised expectations of using this data for purposes beyond their intended use of supporting care delivery and compensation, but that it will be important to be clear about the actions, attitudes and policies needed to achieve the benefits. Among these are the need for realistic expectations, appropriate privacy protections, preservation of linkages from health data to external knowledge, accessing the appropriateness of accessing full medical records, and understanding data anomalies ⁵⁶.

Significant progress is being made in adoption of EMR data standards to promote portability and aggregation. For example, the Consolidated Health Informatics Initiative adopts a portfolio of existing health information interoperability standards for health vocabulary and messaging, enabling all agencies in the federal health enterprise to “speak the same language” based on common enterprise-wide business and information technology architectures ⁵⁷.

Overly simplistic analytic methodologies will not produce credible results, especially to detractors of this approach to drug surveillance. In an example of a relatively simplistic methodology, FDA Office of Drug Safety (ODS) epidemiologists collaborating with FDA safety evaluators are reported to estimate how frequently an adverse event occurs among the population exposed to a particular drug, and then compare the estimate with how frequently the same event occurs in an untreated population ⁵⁸. Innovative statistical models and methods for analysis of extremely large datasets (large number of observations or large number of dimensions), an active area of research, will therefore be necessary to supplement and replace more simplistic methodologies such as adverse event frequency comparisons. Research in computational statistics, for example, involves the development of visualization and computationally intensive methods for mining large, non-homogeneous, multi-dimensional datasets so as to discover knowledge in the data ⁵⁹.

Avorn observed another limitation that must be considered. Carefully performed observational studies may provide the best information available about side effects, but propensity scores and other multivariable techniques applied to epidemiologic research cannot always control for all the inevitable selection bias, making the transparency of methods and raw data even more important than in randomized trials. Rather than yielding "virtual randomized trials," the methods available for controlling confounding in observational research can sometimes look better than they work. Thus, these studies can inform our understanding only after their methods have been scrutinized closely, fairly, and objectively — but only if the data are available ⁶⁰.

An extraordinary informatics research opportunity

The Committee on the Assessment of the US Drug Safety System of the Institute of Medicine has written that:

...the committee believes there is an abundance of extraordinary research opportunities that could substantially enhance the [FDA's] regulatory processes with respect to both the efficacy and safety of new therapeutics. Many of the opportunities involve the creation of new algorithms and methods to improve the processes of preclinical and clinical drug development and new processes to enable effective safety and efficacy monitoring and evaluation over the entire lifecycle of a therapeutic ⁶¹.

A pilot EMR-based project in the domain of drug adverse events surveillance, conducted through centers of excellence including large medical centers that have gone or are going electronic, in collaboration with the pharmaceutical industry and perhaps with federal support from NSF (which offers Grant Opportunities for Academic Liaison with Industry) ⁶² or other relevant agencies, would be an useful way to develop solutions to some of the challenges raised. As a start on such a clinical surveillance infrastructure, EMR systems at selected major medical centers, with research into adaptations for ongoing drug surveillance, could be leveraged via periodic EMR data aggregation and sharing with researchers and regulators for analysis. Of course, data would need to be de-identified to protect patient privacy and confidentiality and comply with laws and regulations such as the HIPAA Act. This data may help the pharmaceutical industry, government and the consumer sectors prevent harmful medicines from remaining on the market for an excessively long time.

Other advanced healthcare initiatives might be accelerated as well. For example, EMR clinical data could also be combined with genetic data to aid pharmacogenomics, the study of the effects of individual genetic variations on drug response. Such efforts are aimed at the development and prescribing of drugs that maximize benefit and minimize side effects in individuals, as well as “drug salvage” of compounds withdrawn due to serious side effects in genetically vulnerable population subsets. The legitimacy of off-label drug use (use for conditions other than which the drugs received FDA approval), a common phenomenon involving more than 100 million prescriptions in the United States annually⁶³, could be verified or disproved. These are just several examples of capabilities that would be quite valuable, both clinically and economically, to both consumers and the pharmaceutical industry.

Considering the seriousness of the problems with pharmaceuticals, these enhanced drug surveillance processes should be explored to reduce or alleviate the need for current inefficient, prolonged post-marketing clinical trials (performed somewhat unwillingly by the industry) on a relatively small number of patients as mentioned earlier, and could grow in size and scope as national EMR implementation grows. EMR modifications to address other issues in informational quality (e.g., blinding, reduction of terminology usage variations) are possible and should be explored.

As EMR domain experts, Medical Informatics professionals can make valuable contributions to use of EMR in drug surveillance, as well as in efforts to enable or improve disease management, bioterrorism and early epidemic detection, and related areas.

In conclusion, developing a capability for drug post-marketing surveillance on a societal scale is a grand challenge that is approachable, achievable, and has implications towards those developing and/or using medications. Such research would also provide an excellent test bed for solving the technological, informatics, and organizational issues towards other broad domains of surveillance utilizing large-scale EMR.

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