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Registries, research, and regrets: is the FDA's post-marketing REMS process not adequately protecting patients?

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Introduction

Regulatory science in the United States is barely a century old, with its genesis in the 1906 Pure Food and Drugs Act [Hamburg, 2010]. In 1993, the US Food and Drug Administration (FDA) initiated the MedWatch program, with the aim of 'embedding reporting into the culture of medicine' [Kessler, 1993]. The remedies for shortcomings in that program [Smith *et al.* 2006], targeting medical products with specific safety concerns, were RiskMAPs (risk minimization action plans), established in 2002 (see Table 1) [FDA, 2005].

The 2006 Institute of Medicine report [Shane, 2009], and subsequent efforts by the FDA, the Agency for Healthcare Research and Quality, and the translational research community, resulted in RiskMAPs being superseded by the Risk Evaluation and Mitigation Strategies (REMS) program, incorporated into the 2007 FDA Amendments Act [FDA, 2008a].

REMS programs, as currently mandated, can incorporate several components, including registries, medication guides, patient package inserts, communication guides for healthcare providers and educational material to ensure safe use of the product [FDA, 2008b]. The reporting of serious adverse events to the FDA is still not a mandatory aspect of the REMS strategy *per se*, although the FDA is required to file quarterly reports based on biweekly screening of its Adverse Event Reporting System concerning REMS-associated therapies. To improve the postmarketing quality improvement process, it included optimizing input into the MedWatch program, more black box warnings and the Sentinel Initiative [FDA, 2008b; Federal Register, 2007]. As Leiderman has pointed out, 'The "new" risk management approach expands the historic roles of industry and government as providers of product safety and prescribing information [through the product label] to a more "active" approach introducing special tools and programs to support safe use of selected products' [Leiderman, 2008]

Diplomatically skirted in this innovation process (and the FDA Commissioner's recent Shattuck lecture) [Hamburg, 2010] is a critical issue: the opportunity to gather medical information about the product and its risks from the entire postmarketing at-risk population. Given that option, it is possible to use this patient cohort's experience as the study group for new questions posed concerning that experience after commercial release.

When is the exploitation of such remarkably rich datasets to be considered research, and thus amenable to the reporting requirements, along with checks and balances on control of that reporting,

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Table 1. Possible formats for RiskMAPs (the strength of the safeguard increases from top to bottom of list).

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Education and outreach: medication guides for patients, continuing-education programs for healthcare providers
Reminder systems: prompts, reminders, double checks, or guides for healthcare providers, patients, or both
Patient education with acknowledgement or use of informed consent forms
Healthcare provider attestation or acknowledgement
Performance-linked access systems:
- Prescribing and dispensing only by specially trained and certified healthcare practitioners
- Dispensing only under conditions that meet evidence-of-safe-use requirements
- Mandatory enrollment or registration of patients, prescribers, or pharmacists in restricted drug distribution programs or registries
- Drug administration in special settings

Reproduced from [Shane, 2009].

that protect human clinical research subjects? And, in the internet age of instant access to large amounts of data, instant feedback and communication over large networks of people and resource assets, can we do with anything less? I write as an academic medical center-based neurologist actively involved in clinical research of the causes and treatments for multiple sclerosis (MS). I am concerned about the lack of policy guidance, in certain special circumstances, to those who finance and conduct the translational research that brings drugs to market. There are economic and ethical reasons, some defensible, and some not, for the present way we survey for toxicity in the postmarketing treated population. This essay is offered as one physician's position on the way to best establish ongoing patient safety in using new therapies with rare but high-risk complications.

This essay will introduce the following points: there is a place for considering research aims in the context of the REMS process for certain drugs. Natalizumab's (Tysabri, Biogen Idec) example of an MS therapy with a novel mechanism of action and a rare and very serious complication is used to argue for such an expansion of the legitimate aims of a mandated registry. There are important differences in policy, financing, design and implementation among clinical trials with predefined endpoints and restrictive qualifying criteria to reduce confounding variables, and studies done on a prospectively accruing population. However, the present and increasingly more complex state of MS therapeutics – clinically, immunologically, ethically, financially and politically – demands a renewed approach to differentiating the passive REMS registry and the exploitation of the population at risk to further scientific and healthcare goals. Recommendations are made concerning the ways the patient, scientific, healthcare and policymaking communities can operationalize and synergize their goals and communication. While our purposes do not always coincide, we all should agree, along with Sherman and colleagues that the programs are ultimately in place in an attempt by all stakeholders to supply novel drug therapies while ensuring the highest level of patient protection [Sherman *et al*. 2011].

The RiskMAP/REMS program for natalizumab

Natalizumab is approved for adult patients with relapsing forms of MS. It was temporarily withdrawn in February 2005 due to postapproval reports of the association of its use with the rare brain infection, progressive multifocal leukoencephalopathy (PML). Its relaunch in July 2006 was allowed after the enacting of a RiskMAP. Its registry, Tysabri Outreach Unlimited Commitment to Health (TOUCH) (see Table 2) [Office of Drug Safety Natalizumab RiskMAP Review Team, 2006] had risk assessment goals including determining the incidence and risk factors of PML [Public Health Service, undated]

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As noted by Rita Shane [Shane, 2009], such performance-linked access systems provide increased safeguards by limiting access of target populations to drugs with increased risk along with benefits. A pregnancy registry and an 'enhanced' research-based monitoring registry (TYGRIS), following 5000 patients in the USA and Europe, were also established. In 2007, the Tysabri RiskMAP was grandfathered, without modification, into REMS.

At the point of reintroduction to the market, a sponsor spokesperson noted that, while there were clear guidelines on who may stock,

Table 2. Tysabri Outreach Unlimited Commitment to Health (TOUCH) program risk minimization and assessment goals [Public Health Service].

To promote informed risk–benefit decisions regarding Tysabri use in the treatment of patients with multiple sclerosis
• Prescribing physicians, and consequently their patients know that Tysabri is associated with an increased risk of PML.
• Physicians prescribe Tysabri only for treatment of multiple sclerosis
To minimize the health consequences of PML (e.g. death, disability)
• Prescribing physicians know how to diagnose PML and know to suspend Tysabri dosing immediately at the first signs or symptoms suggestive of PML.
• Patients should know to promptly report to their physician any continuously worsening symptoms lasting over several days.
To minimize the risk of PML
• Prescribing physicians know that Tysabri is contraindicated in patients who are immunocompromised.

PML, progressive multifocal leukoencephalopathy.

purchase, supply, deliver and receive natalizumab, there were no similar 'rules of engagement' for how the data emerging from the program would be shared with the FDA; how and on what timeline its findings and process were to be reviewed; and how modifications it required would be adopted to better meet the program goals [Bozic, 2009]. TOUCH has no explicitly defined experimental procedure or therapy, nor a research design to explore treatment of individuals or the group of registered patients. It requires signing of an assent form by the physician noting the eligibility and successful process of informed consent, and by the patient, who acknowledges the known risks for PML and the use of their personal medical information. Submission to an institutional review board was not required.

TOUCH REMS reporting includes health outcomes data (e.g. PML rate, overall safety), systems/process data, quality and compliance metrics [Public Health Service, undated]. There is no mandate for the program to report to the doctors prescribing the drug, or to the patients receiving it. The feedback loop that would have allowed a dynamic, evolving process of asking clinical or scientific questions about the population at risk, and acting on answers to those queries in clinical practice, was not completed.

Since mid 2009, the sponsor's website and their liaisons have had variable amounts of updated information available concerning PML cases. The removal of information previously posted concerning their management may have coincided with the 3-year RiskMAP calendared sundown for event reporting. This has been remediated more recently on the sponsor's website for physicians [Biogen Idec, 2011]. There has also been commendable research reported on the usually commensal human polyoma JC virus, the causative agent of PML, its conversion to a neurovirulent form, and its method of passage into and infection of the central nervous system, as well as the use of plasmapheresis and other treatments in clearing the drug and infection from the system [Chen *et al.* 2009; Lindå *et al.* 2009]. This slow accumulation of critical data has been promising, including new subcohort prospective analyses of diagnostic testing of blood for the PML agent. But with one exception these have failed to exploit the entire TOUCH cohort as a resource [Major, 2009]. There are nearly 80,000 patients receiving this drug worldwide, and actually more than 40,000 in the USA as of the time of writing. By design, the numbers to establish prospective safety data passively in the TYGRIS trial ($n = 3000$), and the 1000 patients in STRATIFY-1 to follow users of Tysabri with positive and negative JC virus antibody tests for 2 years for development of PML, and the 8000 in STRATIFY-2 to establish the prevalence of JC virus antibody positivity and accuracy of the blood test in the naïve population, are veritable tips of the iceberg of data one could glean from such a population under treatment. The point is not that these studies are not fine ways to ask a scientific question, model the statistics, and get a yes or no answer to the null hypothesis posed. It is that there is far more that one could do, that has not been done in the USA, using the total population under risk.

It can be argued that the sponsor did what it could to release safety information. It no doubt had to contend with counsel that defined such publication, on websites, however restricted for access, as promotional material, *versus* scientific abstract or simply disclosure of relevant data to a

concerned medical community. As such, different prepublication reviews and approvals by oversight bodies would be required. The observer of the process over the last several years has noted a dizzying variability to the quality, quantity and depth of analysis of the data made available by abstract at conferences, PR releases and verbiage on websites for investors, websites for healthcare professionals and formal publications. The back-and-forth bowdlerization of information that had previously been provided in some versions of real-time reinforced the impression that access to timely and relevant safety data was being compromised by the sponsor's varyingly restrictive policies on data sharing.

Presently, the FDA's premarketing approval of a medical product has been the imprimatur of the adjudicated safety profile. However successful the initial review and registration process has been, safety issues are constrained by data derived from phase III clinical trial designs powered to demonstrate efficacy. Rare but predicted events can be missed in this process. Something about the natalizumab experience seemed to have highlighted a weakness in the system's capacity to oversee safety.

Registry programs in multiple sclerosis, and the (relative) uniqueness of the natalizumab challenge

REMS and their registries are new phenomena; they are still being defined for their usefulness and the probity of the divisions they create in fiduciary and ethical obligations borne by a therapy's stakeholders. Their requirements are only met with time and resource costs to all of them. In addition to increasing the role of the government in the supervision of medical care, they also increase the amount of required postmarketing effort. Although this mostly hits the resources (and pocketbook) of the drug company, these programs can also strain the resources of treating physicians. Minimizing registry-specific activity required of the practicing physician likely increases compliance and recruitment success. These strategies have contributed to the lowered expectations for the epidemiological and clinical research that these registries might support. Most doctors do not operate in a research environment, and the demands of investigational research are not good fits with busy clinical practices.

The US medical community has treated patients under registries other than TOUCH (16 as of March 2008) [Federal Reigister, 2008]. In each case, specific criteria identified the principal stakeholders, the data collection protocol, and what would be analyzable for appropriate safety oversight. Natalizumab, for reasons I will profile below, represents a unique challenge that forces us to confront the question anew. And, importantly, its issues — rare serious adverse events requiring explication, a registry representing total ascertainment of the population at risk, a disease and therapy seeking additional evidence for variable pathogenesis and treatment mechanism and response — are those that the MS community will likely face with many of the therapies reaching the market in the near future.

Defining the TOUCH RiskMAP/REMS process as research

The case of natalizumab among therapies provided with REMS protections is unique in how its toxicity and that toxicity's management are evolving, moving targets. Surveillance and vigilance protocols for the diagnosis and treatment of PML are still being developed. Patients are being diagnosed and treated for PML without timely explication of the prior events to the treating community, including critical information such as up-to-date incidence numbers or events leading up to and then following diagnosis, the treatments used and their success. Those outcomes apparently fall along on a broad spectrum of resultant disease severity and outcome. Reporting these outcomes is not part of the defined REMS process, and as such these data are not considered to fall under disclosure requirements that would be demanded of research. The sponsor's website physician-only updates recently disclosed that as of 4 May 2011, there were 124 confirmed cases of PML since the reintroduction of Tysabri, out of about 83,000 treated patients. Risk factors for PML, such as prior exposure to other immune-suppressive agents, are derived from the TYGRIS dataset, and, as the website points out, that '*groups' experience may not represent that of the larger TOUCH population*' (emphasis added) [Biogen Idec, 2011].

Clear failures to exploit large datasets collecting information on drugs with mandated REMS programs have occurred in other cases. Recent reports noting an increased risk for ulcerative colitis in users of isotretinoin (Accutane, Roche

Holding), established that risk by canvassing large managed care databases for the disease and then identifying contributing demographic and concomitant health factors. The Accutane RiskMAP, which was established to ascertain significant toxicities of the treatment, specifically pregnancy, could not be utilized [Roan, 2009].

In the case of natalizumab, it can be argued that no further specifics concerning cases need be promulgated as long as the incidence of PML does not exceed that which is documented in the FDA-approved product insert. This logic appears to derive from the following, to my mind, poorly supported assumptions: cases of PML have no distinguishing characteristics, by history, presentation, testing, or outcome, that can meaningfully contribute to risk–benefit decisions made concerning natalizumab's use; every case of PML, once noted, required no detailed follow up shared with prescribing doctors; raw data – that is, information on a case-by-case basis - serves only to draw attention to the negative aspects of the drug, overemphasizing issues that are of potential harm to the informed consent process, and to the sponsor, without contributing scientifically or clinically valid information to treating physicians; and there is no moral or legal standing for the argument that physicians are vulnerable to an accusation of malfeasance in performance of medical care if such information is theoretically available, but embargoed by the data owner. The sponsor has made due diligence efforts to inform the medical community about the issue, but it is obvious from the sporadic and variable quality and quantity of the results of those efforts that they are contending with a complex intracorporate set of stakeholder priorities concerning that disclosure process.

When should we be redefining registries as research?

The present natalizumab treatment paradigm is presenting us with an opportunity. We can use it to help establish precedents in patient protections and optimal care using medications that are associated with rare, severe, emergent and poorly understood risks that will only be explicated as the medicines are prescribed. It will be critical to establish that threshold at which the passive, postmarketing registry must be considered research. We are aided to this end by the definition provided by the World Medical Association's Helsinki Accord [World Medical Association, 2008]. This living document, which was created to globally guide the ethical practice of medical clinical research, defines research as that effort involving human subjects that seeks to:

> understand the causes, development and effects of diseases and improve preventive, diagnostic and therapeutic interventions (methods, procedures and treatments). *Even the best current interventions must be evaluated continually through research for their safety, effectiveness, efficiency, accessibility and quality* (emphasis added) (para A.7).

Can we accomplish this latter challenge with the requirements presently in place guiding postmarketing surveillance? As both RiskMAP and REMS legislation recognized, not all such postmarketing evaluations can be adequately performed without full ascertainment of the exposure population, or without incorporating even severely limited protocol-driven data collection, analysis and standardized care into the postmarketing drug-delivery process. When does this crossover from passive data collection, or the process of quality assurance, to a reasonable exploitation of the information that must qualify as medical research?

Not to single out just natalizumab, the recent approval of fingolimod (Gilenya, Novartis) includes a REMS that does not mandate the reporting of adverse events to the sponsor, the uses to which those data may be put, or the questions that can be asked of the dataset [FDA, 2010]. Given the number of systemic complications possible with this first-in-class therapy, could similar arguments for a dynamic, iterative tracking system be made? For pipeline drugs such as alemtuzumab (Campath, Genzyme) and cladribine (EMD Serono), with known and significant potential short- and long-term toxicities, how would a full ascertainment REMS research registry help regulatory authorities feel more comfortable in allowing such therapies to come to the market?

Risk, research and the physician's ethical obligations

The REMS registry-as-research issue has a larger referential frame that might be considered. It imbeds the clinician's work on behalf of a patient under the umbrella of data collection aimed at understanding how to better treat all patients, including those never met (nor billed) by that doctor. This may force a restating of the

physician's sphere of concern. On the one hand, if the concern lies only with the individual patient, is the available data, and the process of its explication, satisfactory to allow ethical care of that patient? On the other hand, if, as this essay suggests, one also has a responsibility to contribute to the management of all patients using the drug through participation in data and testing enquiry and analysis of a REMS registry, does this require redefining a physician's ethical obligations, and the treating and fiduciary relationship, to that population?

There is more time and effort obligation on the part of the patient as well. On the plus side, this could be a perceived benefit to a patient who, as a research subject, feels a closer bond to the prescribing physician, and the personal investment (and placebo effect?) in the goals for the therapy – which may increase the number of patients willing to participate.

And who should be 'watching the watchers' in these circumstances? The present process has created another layer of critical ambiguity – the role of oversight committees like institutional review boards charged with safeguarding patients' health and their rights. Their participation may redefine the relationships of doctors, patients, institutions, government and drug company, in the sharing of risk and fiduciary duty in such efforts. Andrews and colleagues point out that little if any research to establish whether REMS programs succeed at their stated aims has been published [Andrews *et al.* 2009]. There is a built-in paradox to the process: even though the information derived from such programs is presumably to safeguard public health and inform the healthcare community in future decisions about product safety, REMS data are not published as research. The Department of Health and Human Services Office for Human Research Protections (OHRP) has opined that the results of mandatory monitoring programs, or analyses of REMS programs, should not be considered research and therefore may not be published in the scientific literature [Andrews *et al.* 2009]. The resolution of this and the other issues discussed here requires careful consideration of who is at risk, who is asking the questions about that risk, how those questions are asked, with whom are the answers shared and what is expected of that process that impacts on patient safety.

No one argues that, unless under a mandate to commit more resources, there are REMS that should require only passive data collection. It is also inappropriate to expect FDA oversight to substitute for good medical judgment. And, bless the heart of the mercantile post-Keynesian global economy, the ethical issues of beneficence, justice and autonomy defining right conduct in human subject experimentation are not what the marketplace wakes up every morning trying to comply with while marketing and selling approved products.

At the level of neurological clinical practice, we acknowledge that there is always some opacity to risk assessment. The decision to consider certain aspects of medical practice as inherently experimental is problematic. By its very nature, our work as clinicians necessitates an artful concatenation of certainty and uncertainty. Perhaps there is a need to revisit what threshold is required, given the uncertainty concerning the responsible prescription of a new therapy, to move from assent forms to an institutional review board overseen research protocol, complete with necessary institutional checks and balances, reporting requirements, privacy issues and commitment to participant safety.

On a point of sober realism, it might be said that US healthcare consumers exist in a healthcare market, not a healthcare system. As such, it is in the tension creating the separation of powers between the relevant spheres of influence – represented by patient, community, physician and his/her institution, sponsor/pharmaceutical company and government oversight – that the balancing of commitments and interests, and rectitude of the resulting actions, find their dynamic equilibrium. The formation of registry research consortia might only succeed if we achieve an equitable balance of interests and commitments of the stakeholders.

Further iteration of the definition of research for patients in practice may be required

How we face this challenge will define our community's commitments and goals. The World Medical Association could consider once again a modification of the Helsinki document to expand on the need outlined here. We also have the opportunity to apply the new National Institutes of Health mandate for translational research in support of such praiseworthy and community-minded efforts. And, in the age of a

Table 3. Recommendations for expanding a registry to a responsive research-based safety program.

Timely and updated reporting on as complete an understanding of the circumstances of sentinel events.
Incorporation of a safety committee which would expedite feedback and guidance regarding the value of the new information.
Obtain the best possible data both prior and consequent to a sentinel event, with protocols dictating an evolving set of tests and information gathering to allow standardization and modification of what can and should be known about the toxicity and its management.
Research designs, and open- and closed-ended informed consent for such open-label mandatory registries.

diminishing role for academic medical centers to conduct clinical research in partnership with the commercial sector, it may redefine what roles those centers play. For example, an academic MS clinical researcher might have registry participants coenrolled in parallel with the participant's treating neurologist, to perform necessary REMS research activities. In many ways this mirrors the structuring of specialty care for cancers in this country by the National Cancer Institute, and how patients with MS are cared for in more centralized healthcare systems in the European Union [Holman *et al.* 2010].

Table 3 summarizes some of the ways that a REMS registry such as TOUCH might be modified to satisfy the needs we have identified. Obtaining statistically robust findings in such a large cohort as represented by the TOUCH registry demands careful tailoring of the hypothesis-testing design of specific questions to be asked. The heterogeneity of the population can be expected to create bottlenecks and constraints on how this can be properly done. A distributed research network model, such as that done for the Meningococcal Vaccine Study, may be relevant in designing research in this setting, as well as exploiting the FDA Sentinel Initiative's promise [Valentgas *et al.* 2008].

Conclusion

The pharmaceutical industry is in the business of making drugs, and accruing profit for its financial stakeholders in the commission of that work. Of necessity, however, it has an untidy and problematic set of partners – the treating physicians, and the patients who receive their treatment. Companies are unable to reach scientific and marketing targets without fusing their goals with those of the physicians who use their products to treat patients. These physician partners are ostensibly motivated more by selfless sharing of their expertise than by fungible profit, and are the advocates and protectors of their patients, and in some ethically complex way, for the whole community of patients. Government organizations are responsible for the oversight of the safety of human subjects in research, and to minimize the risk of new medical products to the population at large when those products are marketed. They also oversee the maintenance of ethical standards for professional bodies, such as physicians and medical care workers, and the justice system helps define and enforce the laws that support those standards.

These sectors of healthcare are shriven by unresolved ethical and financial contretemps. Issues concerning conflicts of commitment and interest separate the treating physician and the medical community from their partners in the research, development and marketing side of the medical–industrial complex, and harrowing and sometimes draconian legislative actions have been taken to resolve them. The control of information about clinical experience in the postmarketing environment is undergoing a reevaluation as those conflicts are managed and minimized.

The evolution of the REMS process for acquiring and disseminating information and knowledge concerning the uses of drugs with novel mechanisms of action and emergent, rare, poorly described risks can emphasize the responsibilities we share, and reduce strained relations between the stakeholders in that drug's success. The issue is not specific to natalizumab; the scenario will be repeated many times over as more drugs are approved and brought to the market with rare and serious but poorly understood complications.

Clearly, our questions also pertain to the conduct of human subject protection and research oversight by responsible institutions. Conducting medical experiments on humans in a postmarketing, mandatory-enrollment registry, with evolving ways of evaluating the efficacy and safety of that intervention, may require oversight that exceeds that of quality assurance programs which are voluntary and have specific predefined interventions and aims.

Physicians will need to define the relevance of data derived from such registries. We will need to answer questions such as who owns that data, and who has the right to exploit it, to disseminate resulting analyses, and in what form. How far are we willing to alter our medical practices in order to comply with the systemic requirements of programs? And who will pay for it? Revisiting the REMS plans which allow us to pursue our common goals will go far in bridging the gap between the concerns of treating physicians, the governmental and institutional oversight of patient safety and rights, and the sponsor's desire to be a good citizen as well as a profitable commercial entity. And the patient will benefit.

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