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Will Risk Evaluation and Mitigation Strategies Ever Be Accepted?

It has been roughly 3 years since legislation was signed into law that gave the FDA authority to require drug manufacturers to provide a Risk Evaluation and Mitigation Strategy (REMS) for certain drugs. The FDA Amendments Act of 2007 (FDAAA) was a response to the public's focus on drug safety, highlighted by high-profile cases such as rofecoxib (Vioxx) and rosiglitazone (Avandia).¹ Notably, however, oncology practitioners have dealt with REMS for much longer than 3 years. Thalidomide's risk management plan was in effect years before the FDAAA was passed, and was "grandfathered" into officially becoming a REMS in 2008.²

Recently, oncology practitioners had to navigate an expansion in the number in drugs requiring a REMS. Although the REMS component is most often a medication guide, a number of important or widely used oncology drugs have "elements to assure safe use" (ETASU). Perhaps the most well-known of these is the ESA APPRISE Oncology Program for patients with cancer who receive the erythropoiesis-stimulating agents (ESAs), epoetin alfa or darbepoetin alfa. Oncology practitioners will further be impacted by the recent announcement that the FDA will require a REMS for all long-acting opioids.³ With mounting experience and ever-expanding programs, the important question is: will providers ever accept REMS?

Evidence for the answer can be found by looking back to 2010, when NCCN held a REMS Work Group and Policy Summit that culminated in a White Paper published as a supplement to *JNCCN*.⁴ The White Paper detailed survey results about provider familiarity with, workload as a result of, and perceptions of REMS. The survey was sent to a pool of clinicians registered on NCCN.org and who have opted in to receive NCCN Trends Surveys. In April 2011, NCCN conducted a follow-up survey using the same methodology and questions to see if attitudes had changed after 1 year (both surveys went to the same recipient pool; of the 599 respondents in 2010, 64 also answered the 2011 survey).

The results were interesting in that, overall, the percentage of respondents indicating that they were "not familiar" with REMS increased from 20% in 2010 to 24% in 2011. When these data were split by provider groups, the upward trend was seen among physicians and nurses. However, the percentage of respondents who claimed that they were "very familiar" with REMS also increased across all groups (Figure 1).

The survey also looked at physician participation in certain REMS programs for which registration is required and asked respondents to indicate if they were currently registered, planning on registering, or not registered with no plans to register (Figure 2). Participation in these REMS programs for lenalidomide and thalidomide were about 90% in both years. For ESAs, participation increased from 41% in 2010 to 92% in 2011, probably because the ESA APPRISE program was unveiled 1 month before the 2010 survey was administered. Participation in the REMS program for fentanyl buccal film was consistent and low in both surveys.

Perceptions about the impact of REMS on patient safety, provision of patient care, and access to medications was surveyed as well. In the 2010 survey, fewer than half of respondents believed that REMS will improve patient safety (39%), and about half believed that REMS will better inform patients about drug risks (51%). Conversely, more than half believed that REMS will interfere with provision of patient care, drive use toward drugs without REMS, and create or worsen disparities in care (55%, 60%, and 53%, respectively). The 2011 survey indicated slightly more optimism, but results were not much different (39%, 57%, 50%, 55%, and 46%, respectively).

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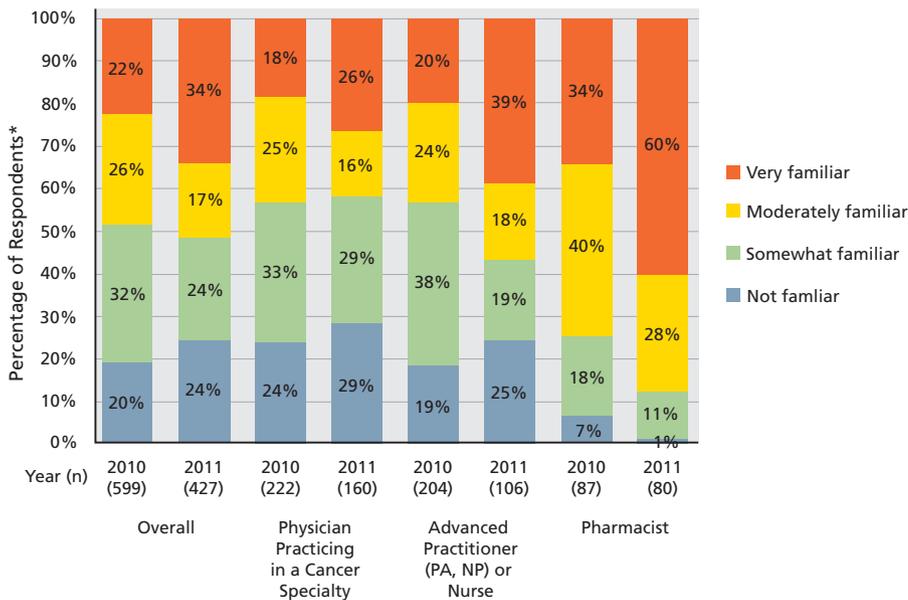


Figure 1 Survey results: familiarity with Risk Evaluation and Mitigation Strategy (REMS) regulations and the different components of REMS.

*Not all percentages total 100%, due to rounding.

Regarding the original question of whether REMS will ever be accepted by oncology practitioners, do the high rates of participation in the various REMS programs suggest that providers have come to accept REMS?

The Unified Theory of Acceptance and Use of Technology (UTAUT) may offer insight. This theory is used in the information technology industry to model acceptance of new technologies. We can extrapolate and assume that REMS is a new “piece of technology” used to mitigate risks of certain drugs. Thus, we can apply the 4 domains proposed by UTAUT that directly influence whether and how people will accept and use a new technology: 1) performance expectancy, 2) effort expectancy, 3) social influence, and 4) facilitating conditions to REMS.⁵

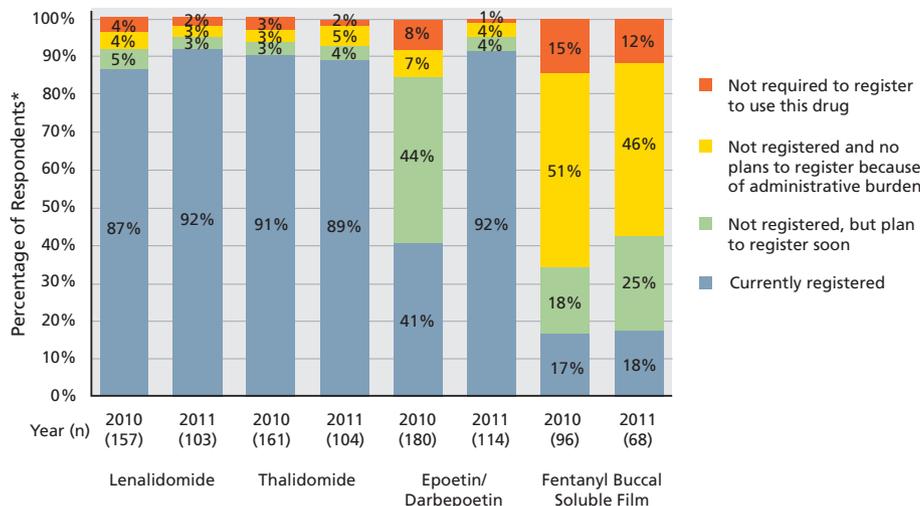


Figure 2 Survey results: physician participation in Risk Evaluation and Mitigation Strategy (REMS) programs for specific drugs with elements to assure safe use.

*Not all percentages total 100%, due to rounding.

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The definitions of these domains, as well as how they affect user acceptance, are straightforward. In the context of REMS, *performance expectancy* would be defined as “the degree to which an individual believes that using the system will help” mitigate drug risks. *Effort expectancy* is “the degree of ease associated with the use” of the REMS requirements. *Social influence* is “the degree to which an individual perceives that important others believe he or she should use the new system.” Finally, *facilitating conditions* is “the degree to which an individual believes that an organizational and technical infrastructure exists to support use of the system.” This definition is not readily applicable to REMS, but one interpretation can be the degree to which REMS is compatible with all aspects of current work, including patient care.⁵

The UTAUT states that performance expectancy is the most influential domain for user acceptance. However, the NCCN Trends Survey results and anecdotal accounts suggest that this is not the case with REMS. Rather, the acceptance we observed is most likely due to social influence; a higher authority mandates that prescribers must comply with REMS requirements to provide that drug (in this case, thalidomide, lenalidomide, and ESAs) to patients.

The NCCN Trends Survey data suggest that the performance expectancy of REMS is mixed. Although most respondents believe that REMS will better inform patients about drug risks, a minority believe that REMS will meet their overall goal of improving patient safety. We have also heard from numerous colleagues that the administrative tasks (i.e., effort expectancy) with REMS are too burdensome. Additionally, the survey suggests that clinicians believe REMS will interfere with the provision of patient care and drive use toward drugs without REMS, indicating that the facilitating conditions for REMS are suboptimal in the eyes of providers.

Based on this theory and the information collected, can we state that prescribers have come to accept their fate with REMS purely because of social influence (i.e., because the law mandates us to do so)? Before we can, an important caveat to this theory must be mentioned. Simply stated, social influence in mandatory settings causes users to comply with a new technology in the short term. However, the UTAUT authors state that “this normative pressure will attenuate over time as increasing experience provides a more instrumental (rather than social) basis for individual intention to use the system.”⁵ This explains the early adoption of REMS by health care practitioners, but it also means that this adoption could be short-lived.

Thus it is possible that some providers will decide not to participate in any REMS programs. Instead, they may decide to use alternative therapies or refer patients to providers who do participate in REMS programs. We can see evidence of this in the low participation rates with REMS for fentanyl buccal film, a treatment option for which other effective alternatives are available. Using this type of analysis, various professional organizations, including NCCN, have raised the significant concern that REMS could create disparities in care.^{4,6}

It appears that the only way to avoid this scenario is to improve providers’ perception of the benefit of REMS, reduce the administrative burden, and better integrate REMS into the current workflow of caring for patients. The FDA should make every effort to demonstrate, scientifically, the benefits (or lack thereof) of REMS programs on mitigating drug risks. Further, the effort made by providers to meet REMS requirements could be improved by standardizing REMS requirements and integrating them into health information technology programs.

In summary, REMS is still a major concern for oncology providers. Especially with the announcement of a class-wide REMS for long-acting opioids, the list of drugs requiring REMS will continue to expand. One piece of good news is that some drugs have been released from REMS requirements (e.g., pazopanib). Further, the FDA appears to have heard the feedback from providers regarding the burden of REMS

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and is considering options to improve these programs. For example, the class-wide REMS for long-acting opioids specifically mentions standardization of processes.⁷ Moving forward, the intrinsic acceptance of REMS by providers will be contingent on minimizing the administrative burden of such programs and demonstrating that they are beneficial for patient care.

References

1. Gottlieb S. Drug safety proposals and the intrusion of federal regulation into patient freedom and medical practice. *Health Aff (Millwood)* 2007;26:664–677.
2. Department of Health and Human Services. Identification of Drug and Biological Products Deemed to Have Risk Evaluation and Mitigation Strategies for Purposes of the Food and Drug Administration Amendments Act of 2007 [notice]. *Fed Regist* 2008;73:16313–16314.
3. U.S. Food and Drug Administration. Questions and answers: FDA requires a Risk Evaluation and Mitigation Strategy (REMS) for long-acting and extended-release opioids. Available at: <http://www.fda.gov/Drugs/DrugSafety/InformationbyDrugClass/ucm251752.htm>. Accessed June 1, 2011.
4. Johnson PE, Dahlman G, Eng K, et al. NCCN Oncology Risk Evaluation and Mitigation Strategies White Paper: recommendations for stakeholders. *J Natl Comp Canc Netw* 2010;8(Suppl 7):S7–27.
5. Venkatesh V, Morris MG, Davis GB, et al. User acceptance of information technology: toward a unified view. *MIS Quarterly* 2003;27:425–478.
6. American Pharmacists Association. White Paper on designing a risk evaluation and mitigation strategies (REMS) system to optimize the balance of patient access, medication safety, and impact on the health care system. *J Am Pharm Assoc* 2009;49:729–743.
7. US Food and Drug Administration. Letter sent to Opioid Manufacturers Outlining Opioid REMS Implementation. Available at: <http://www.fda.gov/downloads/Drugs/DrugSafety/InformationbyDrugClass/UCM251595.pdf>. Accessed June 3, 2011.

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