Risk evaluation and mitigation strategy programs in solid organ transplantation: the promises of information technology

Demetra S Tsapepas, Jaclyn T McKeen, Spencer T Martin, Jennifer K Walker-McDermott, Alex Yang, Jamie Hirsch, Sumit Mohan, Ruchi Tiwari

ABSTRACT
Risk evaluation and mitigation strategies (REMS) required by the Food and Drug Administration are implemented to manage known or potential risks associated with medications and to ensure ongoing safe use throughout the life of a pharmaceutical agent. Healthcare organizations have begun to adopt information technologies with clinical decision support (CDS) to ensure safe use of medications. Systems have been expanded and customized to also ensure compliance with regulatory standards. End users who are unfamiliar with particular medication use provisions are at risk of unknowingly inappropriately fulfilling specific components. Institution-specific customization of vendor-provided CDS is useful to enhance provider awareness and ensure compliance with standards. Integration of health information technology systems to fulfill REMS requirements is novel and important to ensure consistency as healthcare standards evolve.

INTRODUCTION
Approved in 2007, the Food and Drug Administration (FDA) Amendments Act authorized a coordinated, mandatory, and enforceable process for risk mitigation when there are known serious risks associated with the administration of a medication. Risk evaluation mitigation strategies (REMS) were developed to ensure that the benefits of a medication outweigh the risks associated with its use. A REMS program may be mandated during a drug’s approval process or even after FDA approval if safety concerns are noted during post-marketing surveillance or phase IV studies. Post-marketing surveillance has often led to discovery of new adverse events, and may necessitate regulatory action via labeling changes, requirements of disease registries, and now the evolution of mitigation strategies. REMS requirements apply to both innovator and generic formulations of a drug. Fulfillment of the various components of a REMS program can be elusive and cumbersome, and thus integration of such requirements with innovative information technologies can ensure both patient safety and compliance.

Healthcare organizations increasingly use information technologies embedded with clinical decision support (CDS) and medical logic modules (MLM) to enhance medication safety. Computerized physician order entry (CPOE) embedded with care protocols may avoid potential medication-related errors and lead to improvements in efficiency, quality, and safety of medication therapy management. CDS is intended to assist healthcare providers with decision-making by guiding clinician choices through algorithms that fulfill specific requirements of patient care protocols. CPOE and pharmacy information systems with customized CDS with institution-specific MLMs may assist prescribers in adhering to regulatory standards, such as REMS programs, in a structured manner. Customized order sets, a collection of related orders grouped for a clinical purpose, may facilitate standardized treatment, embody a care pathway, or optimize medication use. Order set development within a CPOE system requires multidisciplinary participation, rigorous testing, continual review, and version control management. Its implementation can be difficult, time consuming, and expensive, and may lead to changes in provider workflow. Despite the aforementioned potential barriers, carefully implemented order sets may encourage evidence-based or institution-specific care through the influence of provider behavior.

Currently, there are two immunosuppressive agents used in solid organ transplantation with FDA-mandated REMS programs: belatacept and mycophenolate. Herein we describe our innovative use of information technology to ensure institutional compliance with REMS requirements of these medications.

Belatacept
Belatacept, a recombinant soluble human fusion protein was the first biological agent approved for maintenance immunosuppression after renal transplantation. During the drug approval process, FDA review of efficacy and safety found that treatment with belatacept conferred an increased risk of post-transplant lymphoproliferative disorder (PTLD) and progressive multifocal leukoencephalopathy (PML) among patients without immunity to Epstein–Barr virus (EBV). Approval of belatacept in June 2011 was conditional upon the establishment of post-marketing safety surveillance and a REMS program to ensure that known, serious risks of use were outweighed by the drug’s benefits.

The REMS program involves two components: (1) distribution of a medication guide to patients and (2) a communication plan for healthcare providers and preimplantation planning (table 1).

To ensure compliance with the aforementioned requirements, a customized order entry item and structured note checklist for belatacept was created in the CPOE system at our institution (see online supplementary appendix figures 1 and 2). The entry was built as an order set to facilitate fulfillment of the REMS requirements, ensure safe use, and practice fiscal stewardship. The order set comprises sections to ensure standard order entry components (see online supplementary appendix figure 1, section A), compliance with the REMS requirements (see online supplementary appendix figure 1, sections B, D, and E), and fulfillment of organizational restriction and approval criteria (see online supplementary appendix figure 1, section C). The structured note is embedded with specific elements from the belatacept preinfusion checklist for providers to certify that they have provided patients with a medication guide, educated patients regarding associated risks, and asked questions related to the symptomatology of PTLD and PML (see online supplementary appendix figure 2).

**Mycophenolate**

Mycophenolic acid, an inhibitor of inosine monophosphate dehydrogenase that prevents proliferation of T and B lymphocytes by decreasing purine synthesis, is commonly used after solid organ transplantation.15–17 Post-marketing surveillance revealed first-trimester pregnancy loss (>20%) and congenital malformations (20% of live-born infants) in pregnant women exposed to mycophenolate therapy.18 Due to these safety concerns, FDA required all manufacturers of mycophenolate products to submit REMS proposals irrespective of their long-standing approval (Cellcept [mycophenolate mofetil] 1995, Myfortic [mycophenolate sodium] 2004, mycophenolate mofetil—first generic product 2008).1 19 On 25 September 2012, FDA approved a single, shared REMS for all drugs containing mycophenolate to ensure the safe use of these agents in women of childbearing potential.1 Through education of patients and prescribers, the shared mycophenolate REMS program aims to prevent unplanned pregnancies in patients treated with mycophenolate products, minimize fetal exposure to mycophenolate, and collect information on pregnancy outcomes in transplant recipients.

The program consists of three components: (1) distribution of a medication guide to patients or caregivers with each prescription; (2) specific provider responsibilities related to safe administration of mycophenolate products (table 1); and (3) establishment of a pregnancy registry for women who become pregnant while taking mycophenolate products or within 6 weeks of discontinuing therapy.

Cognizant of the extensive components of the mycophenolate REMS, we used our institution’s CPOE system with CDS algorithms to fulfill the program (figures 1 and 2). We created a customized order-entry form with embedded MLMs for all oral and intravenous mycophenolate entries to guide prescribers through REMS components for female patients between 9 and 59 years of age (institution-specific interpretation of ‘childbearing potential’) (see online supplementary appendix figure 3a), but not for female patients <9 or ≥60 years of age or male patients (see online supplementary appendix figure 3b). In addition, we enhanced our electronic workflow for prescribers by incorporating MLM logic to check for existing laboratory results for β-subunit of human chorionic gonadotropin (β-HCG) in the patient’s electronic health record (EHR) during hospitalization. If the laboratory result was inconclusive or did not exist, we used objects plus programming to automatically add the laboratory test to the patient’s next scheduled phlebotomy time.

**DISCUSSION**

A comprehensive understanding of the medication use process, prescriber order entry, pharmacist review, medication dispensing, drug administration, and relevant regulatory requirements is essential for creating effective electronic healthcare systems. Commercially available EHR systems provide standardized order entry modules from contracted vendors to their clients as a CDS tool. Maintaining, customizing, and continuously evaluating all CDS systems within a vendor-supplied EHR is paramount to optimize patient care and safety. The lack of sharing of

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**Table 1 Risk evaluation mitigation strategies (REMS) program details**

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<tr>
<th><strong>Belatacept REMS program</strong></th>
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<td><strong>Component 1</strong></td>
<td>Distribution of a medication guide to patients before each infusion</td>
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<td></td>
<td>▶ Educate patients about the risks associated with belatacept therapy. The communication plan is directed at healthcare providers whereby safety information is disseminated via professional societies, postings in peer-reviewed journals, and online tools</td>
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<td><strong>Component 2</strong></td>
<td>Communication plan for healthcare providers</td>
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<td>▶ Administering practitioners are required to complete a preinfusion checklist intended to identify patients with signs and symptoms that could be related to post-transplant lymphoproliferative disorder (PTLD) and progressive multifocal leukoencephalopathy (PML)</td>
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<th><strong>Mycophenolate REMS program</strong></th>
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<td><strong>Step 1</strong> Enroll in mycophenolate REMS program</td>
<td>▶ Prescriber training: <a href="https://www.mycophenolaterems.com">https://www.mycophenolaterems.com</a></td>
</tr>
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<td><strong>Step 2</strong> Determine if women of reproductive potential are pregnant at the time mycophenolate is prescribed</td>
<td>▶ Pregnancy testing immediately before mycophenolate therapy is initiated, again 8–10 days after beginning therapy and at routine follow-up visits for the duration of therapy</td>
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<td><strong>Step 3</strong> Patient education</td>
<td>▶ Inform female patients about the serious risks associated with mycophenolate use during pregnancy—patients should be advised to inform their healthcare providers if they are considering pregnancy while receiving a mycophenolate product</td>
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<td></td>
<td>▶ A booklet entitled ‘Mycophenolate REMS Overview &amp; Your Birth Control Options’ is available for distribution to patients</td>
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<td><strong>Step 4</strong> Patient–prescriber acknowledgement</td>
<td>▶ Providers should have their patients or legal guardians acknowledge education (step 3) by signing a patient–prescriber acknowledgment form with the original copy retained in the patient’s medical record</td>
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<tr>
<td><strong>Step 5</strong> Mycophenolate Pregnancy Registry reporting</td>
<td>▶ Providers to report any mycophenolate-exposed pregnancies to the Mycophenolate Pregnancy Registry established to evaluate mycophenolate-exposed pregnancies and their outcomes</td>
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generalizable knowledge about the types and development of healthcare information technology and implementation processes contribute to slow progress in this area.20 Distinct and complex patient populations and unique medication therapies require client-based EHR customization. At present, EHR vendors do not supply CDS tools to fulfill REMS requirements; therefore individual institutions must allocate resources to customize their systems to ensure compliance. Literature describing the customization process and best practices of healthcare information technology in the realm of solid organ transplantation is scarce.21

EHR-based CDS is most effective when implemented within existing workflow processes and integrated with pertinent patient data and hospital guidelines in real time.22 As a center caring for specialized patient populations, we believe that institution-specific customization of our CPOE system is important to maintain compliance with regulatory standards and enforce critical steps that facilitate the safe use of medications. Our approach to CDS customization as described in this report has been instrumental in ensuring the safe and appropriate use of immunosuppressive agents through prescriber compliance with regulatory standards and enhancing patient-centered care through education. In addition, we are able to promote fiscal stewardship by streamlining approval for drug use and ensure safety by automatically ordering necessary laboratory tests before submission of the medication order. We designed, tested, and implemented the CDS system to bring immunosuppressive REMS components to the point of care.

Integrating human factor interactions within CDS algorithms enhances the end-user response and fulfillment of specialized requirements. When customizing CDS, it is important to integrate standard order entry parameters with requirements for compliance with regulatory standards and organizational restrictions. Customizing CDS may be a cumbersome process, as all applicable agents and dosage form entries must be modified individually, as in the case of the mycophenolate REMS process. Due to the evolving nature of medical care in the current regulatory environment, it is imperative to have the ability to quickly modify EHR entries to ensure the safe use of medications.

As the work necessary to integrate CDS algorithms is complex, time consuming, and expensive, it is important to carefully plan the implementation steps. We have described the end products created to fulfill REMS components for belatacept and mycophenolate. Organizations should consider adopting this innovative approach using information technology to ensure compliance with REMS programs. Before we carried out any work, a multidisciplinary team (including pharmacy, nursing, medicine, surgery, and quality assurance) met to develop and review the REMS processes for organizational implementation. The committee developed an algorithm to fulfill the specific REMS components within the constraints needed to enhance end-user satisfaction; the process was then streamlined to ensure that new order entry items were created with new fields, hyperlinks, and text boxes to facilitate prescriber workflow procedures. The specific algorithm for the CPOE system was then shared with the information technology department for development. In the setting of competing priorities and resources, we submitted the specific MLM requirements before the FDA’s initial approval of the REMS criterion to ensure that programming resources would be allocated and ready for implementation. After creation of the CDS logic, we tested individual elements in a sequential manner to revise the algorithms and logic to address inconsistencies with the desired product; this necessitated several exchanges between the requesting committee and the information technology department. After the order configuration information technology team had perfected the design of the new order entry forms, the programmer began constructing new MLMs to be placed on the form. In the case of the mycophenolate entry, we were able to simplify and automate ordering of β−HCG tests to increase the probability of adhering to our policy. To promote internal surveillance, it was decided to use discrete data fields to facilitate the ability to have an effective and efficient review process when assessing compliance with the protocols, institution-specific guidelines, and regulatory mandates if necessary.

Despite significant success with the use of technology to implement these REMS programs, there are still areas for improvement. A next step may be to display the result of EBV and β−HCG tests to the user within the order forms. We had hoped to integrate documentation of patient education into the ordering process (clinicians will likely discuss the education components before ordering the immunosuppressive agent). However, electronic integration of order entry, laboratory

Figure 1 Mycophenolate order workflow. Reprinted with permission from Allscripts Healthcare, LLC.
ordering, and documentation has not advanced to the level of real-time clinician workflow and is a barrier to implementing complete clinical care pathways.

CONCLUSION

The balancing act between meaningful uses of EHRs and interruptive alerts or workflow processes highlights the need for careful planning in the creation and modification of CDS content. Continuous updates to vendor products by a healthcare organization are essential to optimizing patient safety as well as fulfilling regulatory standards, particularly in the care of specialized patient populations. Using EHR with CDS to provide real-time decisions is an effective strategy to improve adherence to institution-specific guidelines as well as REMS programs. This review highlights the importance of close collaboration between EHR vendors and individual healthcare organizations and regulatory agencies to proactively provide enterprise-wide solutions. The benefits of an open architecture to allow relatively quick EHR customization in the setting of evolving initiatives and mandates are also apparent. The ongoing exchange of modifications made to CDS tools will enhance the future of meaningful EHR systems for standards in patient care.

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Figure 2 Mycophenolate laboratory test workflow. Reprinted with permission from Allscripts Healthcare, LLC.
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