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Commentary on Perez et al.: How to Create a 21st Century Adverse Event Reporting System

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Adverse event reporting for patients on clinical trials has two main purposes: (1) informing sponsors and regulators of potential new risks of a given agent, and (2) informing patients and investigators of those risks. While the first goal can help determine the future development of an agent or a class of agents, the latter has the potential to help patients on existing trials or those considering enrolling on an active trial. The analysis of the survey of stakeholders published by Perez *et al.* through the Clinical Trials Transformation Initiative (CTTI) suggests that in oncology, our system for expedited reporting of suspected adverse events are failing on both counts.[1]

The CTTI and US Food and Drug Administration (FDA) present in this issue of *Clinical Trials* a survey which is well conducted, despite its limited scope. Only a handful of sponsors and investigators are interviewed, and there is no indication that they amount to a representative sample. Regardless, the interviewed subjects do provide useful feedback to the changes on the final rule. Clearly, the FDA's revision of the final rule in 2011 was intended to improve the utility of safety reports. In spite of this intent, the FDA has previously reported that the vast majority of expedited reports filed to the FDA are uninformative.[2] The previous analysis and these survey results suggest that we have a long way to go before that changes. The question for the FDA and other regulatory authorities is how cancer researchers can truly inform all relevant parties of the risks inherent in investigational clinical trials and improve the system.

Oncology is a challenging field for a variety of reasons, among them the potentially life-threatening nature of the disease and the risk-benefit ratio that must be employed in cancer drug development. The most active area for cancer drug development involves therapy for metastatic disease. The FDA has been tasked with accelerating drug development for patients with often terminal diagnoses and few available treatment options. As the risk of disease progression and mortality is an ever-present danger for most cancer patients, a higher rate of toxicity may be tolerated in oncology as compared to drug development in most other fields of medicine. That risk tolerance is shaped almost entirely by the potential benefits that may be seen with newer therapies. Patients and regulators may agree that a few

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additional months of a median overall survival advantage may well be worth the potential toxicity, given the alternatives.

The concerns exhibited by Jarow *et al.* and the CTTI survey suggest that over-reporting is the norm. A low threshold for expedited event reporting may be appropriate for drugs that are early in development with relatively few clinical trials. If fewer than 100 patients, or if fewer than 1000 patients, have been treated with an agent, investigators, sponsors, regulators, and patients should take a cautious approach to adverse event reporting. Aggressive adverse event monitoring and expedited filing early in development of a given agent serve to inform all stakeholders of the nature of the risks associated with a drug.

The problem arises from the application of those same principles for agents that have been approved but are currently in clinical trials for additional settings or other indications. One example is the class of immune checkpoint inhibitors, including the FDA-approved agents nivolumab, atezolizumab, and pembrolizumab. One recent article reported that there are over 1000 ongoing clinical trials evaluating the use of immune checkpoint inhibitors targeting programmed cell death protein 1 (PD1) and its ligand PDL1.[3] Some of the existing trials are large phase 3 trials with thousands of patients. How does the final rule apply in these circumstances? For individual investigators holding their own investigational new drug application, the process of sifting through the expedited FDA filings sent to them by their pharmaceutical collaborator must be overwhelming. Given the lack of coordinated effort amongst international regulators and fears of an audit by any of these regulators, multinational pharmaceutical companies are likely forced to over-report, regardless of the efforts of the FDA. Investigators are often receiving multiple reports per day, each of which they must review to determine whether those reports should in turn be sent to their respective institutional review boards and if their trials should amend consent forms, consider a voluntary hold, or simply carry on.

The task of managing and informing stakeholders of the risks of agents which are approved and in common use is simply mind-boggling. As the Jarow *et al.* article suggests and the CTTI survey confirms, the resultant expedited filings to the FDA become an exercise in compliance rather than patient safety.[1, 2] Rather than simply reproducing the same system for all efforts in cancer drug development, perhaps the energy and effort placed into compliance could be harnessed for transparent and immediate reporting to the FDA and even the broader public, at least for broadly-used, marketed agents.

The FDA has several initiatives to evaluate the safety of products which have already been approved, most notably, the SENTINEL initiative, which was originally announced in 2008.[4, 5] Those efforts seek to determine if there is a safety signal for a given agent from electronic health records and other reports sent to the FDA for analysis. While SENTINEL is an ongoing and challenging effort and should continue, clinical trials still provide the overwhelming bulk of the safety data included in the product label. Information technology has and will continue to advance and transform drug development, and the FDA has been forward thinking in taking advantage of new streams of data to better assess both drug safety and efficacy.[6] If the goal of adverse event reporting is to inform the various stakeholders, perhaps the FDA can take a more comprehensive approach to drug safety, at least for

marketed drugs in wide use for which there are ongoing clinical trials. Rather than expediting the reporting of only serious adverse events, all adverse events on clinical trials could be reported with equal speed to both sponsors and the FDA. Those reports could even be made public immediately, giving patients and investigators a nearly instantaneous look at the toxicity seen on clinical trials with a given agent. Pharmacovigilance systems and consent forms could be similarly updated instantaneously, based on all of the currently available data, and an online alert system could be made available so that patients could see any new or emerging data which the FDA deems relevant. As Jarrow *et al.* noted, more deaths due to sepsis for a regimen known to cause an increased risk of infection or even death due to sepsis might not be appropriate for such an alert. However, a new and emerging risk of tuberculosis for patients treated with a particular agent could fall under that category.

The technical challenges of creating an inter-operable adverse event reporting system amongst a variety of sponsors are difficult, but not insurmountable. Indeed, the FDA is already experimenting with sponsors on similar efforts for expedited filing of adverse events.[7] A broad, instantaneous, and public system of adverse event reporting could be limited to drugs which are approved and currently being marketed, which could have the added benefit of giving patients with standard of care therapies the opportunity to learn more about the risks of drugs they are being offered. Further, patient-centered language could be offered so that non-healthcare professionals could understand the nature of these risks.

A separate system of adverse event reporting for marketed drugs would not absolve investigators of all safety responsibility for their trials. For instance, if a particular risk emerged only on a small subset of patients treated on a particular clinical trial, that would be important for investigators and the FDA to determine quickly in order to adequately inform patients on the trial. However, a broader and real-time adverse event reporting system would make compliance a more straightforward activity for sponsors and investigators, while providing information to the public, the FDA, and patients in what would essentially become an online and dynamic drug label and safety database. Investigators and sponsors would still be responsible for categorizing and determining the nature of a given event, so that adverse events are well described, and more importantly, appropriately evaluated and managed.

A real-time adverse event reporting system would require appropriate and periodic review by the FDA and sponsors, but compliance efforts would shift toward providing a comprehensive, real-time view of the safety of a given agent and immediately informing the public and the FDA, rather than sending a torrent of uninformative expedited reports for which no action is expected or taken. Adverse events are an expected and normal part of everyday reality in the world of drug development. Why not harness the tools at our disposal today to make certain that patients are informed of the risks of a given therapy on a real-time and ongoing basis? That would be a system more in line with the spirit of the final rule promulgated in 2011, but it would also be a system truly worthy of a 21st century public health regulator.

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