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Streamlining Adverse Events Reporting in Oncology: An American Society of Clinical Oncology Research Statement

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INTRODUCTION

Monitoring patient safety during clinical trials is critical to protecting research participants from preventable harms as well as protecting patients who will ultimately be treated with an intervention. Under the current regulatory system for investigational new drugs (INDs), sponsors are required to report certain serious adverse events (AEs) that occur during clinical trials to the US Food and Drug Administration (FDA) and all participating investigators through an expedited process.[1] This helps to identify and communicate safety concerns to the appropriate parties as soon as possible.

Despite the critical importance of AE reporting in the drug development process, stakeholders in the system report numerous problems. In the early 2000s, some commercial sponsors of clinical trials began sending AE reports to investigators and to the FDA that do not fulfill the expedited regulatory reporting requirements (Table 1). These AE reports often lack information on whether the reported AEs are relevant to specific trials, are causally associated with the therapeutic agents being studied, or are anticipated events described in the study protocol or investigator brochure. Furthermore, these reports often come without any advice or guidance on the clinical interpretation of the event and the appropriate action to be taken. Thus, researchers, research sites, and the FDA are often left to review a high volume of uninformative AE reports.[3,4] This compromises the detection of valid safety signals and strains resources available for clinical research and for the FDA's review of new treatment applications.

The challenges of AE reporting are magnified in oncology because of the nature of the disease and its treatment. Oncology patients are often ill, many are older adults with multiple comorbidities, and most are treated with more than one therapeutic modality (eg, chemotherapy, radiation, surgery, concomitant medications). Hospitalization is also frequent. Thus, it can be hard to distinguish AEs that result from an intervention during a clinical trial from those that result from other causes.

To address this problem, ASCO hosted a multistakeholder workshop on March 8, 2017, with representatives from academic and community oncology practices, the FDA, the National Cancer Institute (NCI), industry, contract research organizations (CROs), and patient advocacy organizations. The goal of the meeting was to develop a roadmap for making the AE reporting process as meaningful and informative as possible. The concept for the workshop came from the ASCO–American Association of Cancer Institute's (AACI's) Best Practices in Cancer Clinical Trials Initiative, which was launched in 2015 to promote practical solutions to meeting regulatory and administrative requirements for clinical research.[5] This initiative established the guiding principle that existing requirements for research should be "essential for protecting trial participants' safety, promoting the scientific integrity of research, and ensuring efficient trial conduct and adequate resources."[5] The workshop also built on the work of the Clinical Trials Transformation Initiative (CTTI), which has devoted substantial effort to improving IND safety reporting.[6] On the basis of the discussions at the workshop, ASCO developed recommendations for streamlining AE reporting. This article presents the recommendations.

EXPEDITED IND SAFETY REPORTING

One of the FDA's main responsibilities during IND review is to "assure the safety and rights of subjects."[7] The FDA accomplishes this, in part, through ongoing review of AEs in clinical trials of investigational agents.

In September 2010, the FDA published a final rule (2010 Final Rule) on expedited IND safety reporting. The new rule was intended to reduce the number of uninformative AE reports, because sponsors were frequently submitting AE reports in circumstances where there was no evidence that the drug caused the event. Many of the reported events were due to the underlying

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Table 1. Determining Whether an AE Should Be Reported Through the FDA Expedited Process

Term	Definition	Investigator Responsibility	Sponsor Responsibility	Final Determination Responsibility
Serious or life threatening	AEs that result in death, life-threatening situations, inpatient hospitalization or prolongation of hospitalization, persistent or significant incapacity, and so on	Yes (Investigator must report all serious AEs to the sponsor immediately)	Yes	An event is considered serious or life threatening, on the basis of either the investigator's or the sponsor's opinion.
Unexpected	AEs that are not listed in the investigator brochure or those not listed at the observed specificity or severity	No (No requirement to assess expectedness)	Yes	The sponsor is responsible for determining whether event meets the definition of unexpected.
Suspected adverse reaction	There is a reasonable possibility that the drug caused the event.	Yes (Investigator must provide sponsor with an assessment of causality)	Yes (Sponsor's assessment determines reportability, regardless of investigator's assessment)	The sponsor is responsible for determining whether there is a reasonable possibility that the drug caused the AE, taking into consideration the investigator's assessment. The sponsor reports serious and unexpected suspected adverse reaction to the FDA and all participating investigators.

Abbreviations: AE, adverse event; FDA, US Food and Drug Administration.
Adapted from US Food and Drug Administration.[2]

disease, were commonly occurring in the population under evaluation, or were study end points.[8] The 2010 Final Rule revised the definitions for IND safety reporting, introduced the concept of aggregate analyses of AEs, and clarified the requirements for reporting.[1] The FDA also published a guidance document in 2012 and a draft guidance in 2015 to provide additional information regarding its requirements for AE reporting.[2,9]

The current regulatory standard for expedited reporting of AEs is suspected adverse reactions that are both serious and unexpected. Events that do not meet all three criteria (ie, suspected, serious, and unexpected) should not be reported through this process (Table 1). All other AEs are reported to the FDA through sponsors' annual reports.

The 2010 Final Rule defines serious AEs as those resulting in death, life-threatening situations, inpatient hospitalization or prolongation of hospitalization, persistent or significant incapacity, congenital anomaly/birth defect, substantial disruption in the ability to conduct normal life functions, or an important medical event that may jeopardize the patient and may require medical or surgical intervention to prevent one of the previously listed outcomes. Unexpected events are those not listed in the investigator brochure or those not listed at the observed specificity or severity.

Suspected is the most subjective criterion. It means there is a reasonable possibility that the drug caused the event, not that a causal relationship cannot be ruled out. The determination of causality for purposes of reporting rests with the sponsor, not the investigator. This is because the sponsor has access to the most up-to-date and comprehensive information available regarding the drug and is best able to make informed and consistent decisions regarding causality. The determination of causality may consider factors such as the mechanism of action of the drug, the temporal relationship of onset of the AE to administration of the drug, the resolution of the AE on withdrawal of the drug, and whether it recurs upon rechallenge with the drug.

FDA guidance states that single events identified by investigators are usually uninterpretable and should not be reported as IND safety reports unless they are strongly associated with drug exposure (eg, Stevens-Johnson syndrome, agranulocytosis, and so on). Causality is suggested if there are multiple occurrences of events not commonly associated with drug exposure and not common in the study population (eg, tendon rupture). FDA guidance also clarifies that sponsors should not report single events that are serious and unexpected on the basis of known toxicity profile of the investigational drug if they are common in the demographics, underlying disease, or concomitant therapies of the patients. These anticipated events require aggregate analysis to determine if they occur more frequently in patients exposed to the drug compared with those who are not. CTTI has developed a statistical framework that sponsors can use to help judge whether an AE is subject to expedited reporting.[10]

PROBLEM

Expedited safety reports routinely do not meet the requirements in the 2010 Final Rule.[4] This problem emerged in the early 2000s and has continued since, despite the FDA's regulations and guidance and other efforts to streamline AE reporting. Using the expedited process to report AEs that are not suspected, serious, and unexpected creates burdens and inefficiencies for all stakeholders. Investigators and FDA staff are challenged to review all of the submitted reports carefully. It is also challenging to identify AEs that represent new, previously unreported events that are actionable. The overwhelming quantity of data being submitted may obscure important safety signals and, thus, endanger clinical trial participants.

Supporting these concerns, researchers responding to a 2015 survey conducted as part of the ASCO-AACI Best Practices in Cancer Clinical Trials Initiative identified the AE reporting process as one of the most burdensome aspects of conducting cancer clinical trials.[5] Several ASCO volunteer committees also prioritized AE reporting for additional effort by ASCO, given its perceived impact on the efficiency of clinical trials.

CTTI conducted an online survey in 2014 of 201 investigators and investigative staff who conduct oncology clinical trials.[3] Survey

respondents indicated that the workload associated with processing safety reports is substantial and growing. Approximately 80% of sites reported receiving > 20 safety reports per month. Sixty percent of investigators and staff reported that they spend > 10 hours per month processing reports.

CTTI's interviews with 20 principal investigators and other research staff found further evidence of problems in the AE reporting process.[3] Interviewees indicated that safety reports have limited utility and that investigators regularly sign off on reports without reading them. Moreover, none of the interviewees could identify a situation when they used the information from a report to improve their trials or to make patients safer. These results are consistent with a previous CTTI survey that was conducted before enactment of the 2010 Final Rule, where investigators reported receiving too many uninformative reports.[11] Thus, despite the 2010 Final Rule and subsequent FDA guidance, the AE reporting process has not improved for researchers and research sites.

Similarly, the AE reporting process is burdensome for the FDA. Between 2006 and 2015, the FDA's Office of Hematology and Oncology Products (OHOP) received an average of 17,686 expedited IND safety reports per year.[4] The number of reports actually increased after the 2010 Final Rule. An audit of 160 randomly selected expedited safety reports submitted to OHOP in 2015—admittedly a small percentage of the overall number of safety reports[12]—found that only 38 (24%) met all three of the required criteria for expedited reporting. More than half (54%) of the submitted reports were expected events, and in 50% the sponsors did not make any conclusion on causality. Of the 24% that met all three criteria, 42% of the events were anticipated for the population under study. Taken together, these data mean that only 14% (22 of 160) of AEs reported to the FDA were helpful in assessing patient safety. The rest were confusing background noise that wasted resources and may have obscured detection of important safety signals.

Many sponsors have reported recent reductions in the number of safety reports they are issuing. CTTI conducted an online survey in 2014 of 29 clinical trial sponsors: 66% represented large-sized, 10% medium-sized, and 24% small-sized biopharmaceutical companies.[3] CTTI also interviewed seven pharmacovigilance leaders from five global companies. The majority of companies reported generating > 1,200 expedited IND safety reports per year between 2012 and 2014. When qualitatively asked whether they had reduced the volume of safety reports after the 2010 Final Rule, approximately 86% of large company respondents claimed a reduction, generally in the range of 50% to 75%. Mid- and small-sized companies did not report a reduction.

The barriers to sponsors fully implementing the 2010 Final Rule may explain some of the disconnect between sponsors' reported behavior and the FDA, researchers, and research sites' experiences. Barriers identified in the CTTI survey included lack of international harmonization in reporting requirements, liability concerns, difficulty determining causality and reporting thresholds, infrastructure or technological limitations, lack of support for the financial investment required to update internal procedures, siloing of clinical research teams devoted to specific diseases without sufficient cross-company communication, and resistance to changing corporate culture. Sponsors also reported scientific concerns about reviewing AE data from ongoing, blinded, controlled trials, although the FDA recommends that the blind should be broken for reported events.[3]

CROs face challenges similar to sponsors in implementing the 2010 Final Rule. Sponsors often contract with CROs to manage the operational aspects of their clinical trials program, including safety and compliance monitoring. Implementation is further complicated for CROs, however, because of inconsistencies in the services that sponsors request and the format for safety data reporting. In addition, CROs responsible for handling safety reports may not maintain or have access to a sponsor's safety database. In these circumstances, sponsors manually send case data to CROs, which creates inefficiency and the potential for mishandled data.

SUCCESS STORIES OF THE 2010 FINAL RULE

Companies and CROs that fully implement the 2010 Final Rule have dramatically reduced their number of AE reports, which demonstrates that the current regulations can work effectively. Company A reduced its reportable expedited safety reports by approximately 90%, for example, through implementation of new procedures in response to the FDA's 2010 Final Rule.[13-16] To achieve these results, Company A created a new independent functional group with responsibility to assess the causality of serious AEs in clinical trials. As part of a well-supported recruitment effort, it hired multiple highly qualified medical safety review physicians to staff this new division. The new hires brought diverse clinical expertise and industry experience and were assigned to review trials aligned to their therapeutic area of expertise. Company A provided them with intensive training focused on the level of evidence required to support causality assessments and instituted a system for monitoring and reporting compliance, quality, and performance metrics.[13-15]

In addition, Company A established and has maintained consistent thresholds for causality assessments. Its process includes clear documentation of the rationale for all causality assessments. Staff members provide in-depth citations in instances where an AE requires risk communication (eg, investigator brochure update, protocol amendment, informed consent update, dear investigator letter). Staff also classify situations where AEs lack sufficient information to confirm causality and, therefore, do not report these events to the FDA or investigators (as directed in the 2010 Final Rule).[13-15]

Similarly, Company B achieved a 50% to 80% reduction in its AE reports through overhauling its internal procedures.[16] Rather than create a new division, Company B updated its process to address problematic areas it identified in implementing the 2010 Final Rule. This included creating predetermined intervals to review anticipated AEs within a clinical trial as well as using independent teams, unaffiliated with the trial teams, to evaluate the distribution of AEs across trial arms.

Both Company A and Company B have gotten positive feedback on their new approaches to AE reporting from researchers and the FDA. These companies' expedited IND reports now usually meet the criteria for reporting in the 2010 Final Rule. The number of safety reports they issue is in the single digits most months.

RECOMMENDATIONS

Attendees at the workshop brainstormed about best practices in AE reporting for researchers, research sites, sponsors, and CROs and

identified strategies for using technology to improve the AE reporting process. On the basis of these discussions, ASCO developed a series of recommendations to improve the AE reporting process summarized in Table 2.

Recommendation 1. Sponsors and CROs Should Adopt Best Practices for Reporting AEs

Most sponsors have specific teams and processes in place for assessing and managing safety information from clinical trials, although they vary in structure.[17,18] As noted above, several sponsors have made large reductions in the number of AE reports that they send to the FDA and participating investigators through changes to these teams and processes undertaken in response to the 2010 Final Rule. This recommendation is aimed at encouraging all companies to adopt best practices in implementing the 2010 Final Rule.

Recommendation 1.a. Sponsors should fully implement the 2010 Final Rule and only report AEs that are actionable. Practices common to the companies that have made large reductions in the number of AE reports that they send to investigators and the FDA include:

1. A company-wide commitment to reducing uninformative AE reports and focusing time and effort on serious AE reports. Because changing corporate culture is difficult, cross-functional and senior management endorsement is essential.
2. Establishment of a consistent threshold for causality assessments. The threshold should align with the FDA's expectation that AE reports include evidence to support a positive causality assessment, not simply that a causal relationship could not be ruled out.
3. A system for monitoring, measuring, and reporting staff and the overall company's performance in terms of appropriate AE reporting.

Table 2. Recommendations to Streamline AE Reporting

Recommendation	Potential Benefits	Barriers to Implementation
Recommendation 1: Sponsors and CROs should adopt best practices for reporting AEs.		
1.a. Sponsors should fully implement the 2010 Final Rule and only report AEs that are actionable.	Reduces reporting of uninformative AEs Improves compliance with FDA's regulation and guidance Leverages sponsors' comprehensive knowledge about the drug when determining causality	Financial investment Infrastructure or technological limitations Liability concerns Lack of regulatory harmonization Challenge of determining causality and reporting thresholds
1.b. Sponsors and CROs should be receptive to the feedback of the FDA, investigators, and other stakeholders regarding their AE reporting practices.	Reduces reporting of uninformative AEs Improves compliance with FDA's regulation and guidance	Institutional culture Failure of stakeholders to provide meaningful feedback
1.c. Sponsors and CROs should be transparent about their AE reporting practices.	Allows companies to consider sponsors' AE practices before opening a trial Incentivizes the protection of patient safety and efficiency	Loss of competitive advantage or trade secrets
Recommendation 2: Researchers and research sites should adopt best practices for reporting AEs to sponsors.		
2.a. Clinical trials educational programs for investigators should emphasize the importance of reporting serious AEs accurately and completely.	Limits inconsistent and inaccurate identification of AEs and over-reporting	Burden of completing training Perception of need
2.b. Sponsors should recognize and promote the use of centralized training for investigators.	Minimizes the burden of additional training requirements	Sponsor buy-in Lack of regulatory harmonization Variation in sponsors' requirements
2.c. Research sites should adopt and adhere to SOPs for AE reporting that are based on the 2010 FDA Final Rule.	Improves detection, evaluation, and reporting of AEs	No single set of SOPs exists that could be adopted
Recommendation 3: International regulatory agencies should harmonize the regulations for AE reporting.		
3.a. All stakeholders worldwide should support international regulatory harmonization.	Facilitates sponsors' compliance with the FDA and rest of the world's regulations	Challenge of changing regulations, especially country by country
Recommendation 4: All stakeholders should use modern, digital technology to report AEs.		
4.a. A neutral third party should develop a central electronic portal for reporting AEs.	Eliminates fragmented and redundant electronic reporting systems	Stakeholder buy-in Governance Costs

Abbreviations: AE, adverse event; CRO, contract research organization; FDA, US Food and Drug Administration; SOP, standard operating procedure.

4. Clearly written standard operating procedures (SOPs), which require documentation for causality assessments and identification of clinically relevant follow-up information.
5. Highly qualified medical safety review staff who are provided with resources and training for evaluating AEs. Sufficient staffing and clear training allows for consistent assessments and decreases interrater variability.

Adoption of these best practices by more sponsors would likely have a large impact on the efficiency of the AE reporting process and reduce the number of uninformative safety reports received by the FDA and participating investigators. Many companies have not yet adopted these changes, however, despite the FDA's guidance and previous efforts to streamline AE reporting. The major obstacles to sponsors changing their behavior are described in the Problem section above, including the up-front costs associated with changing corporate practices. Nevertheless, ASCO urges sponsors to adopt these best practices, because an improved process is more likely to detect important safety signals, reduce risk to patients, mitigate corporate liability, and improve the overall efficiency of trial conduct.

CTTI has developed an online webinar for sponsors with case studies in AE reporting.[19] Workshop participants have also expressed a willingness to share their experiences and best practices for AE reporting with other companies. Thus, there are existing resources to help companies make the changes recommended here.

Recommendation 1.b. Sponsors and CROs should be receptive to the feedback of FDA, investigators, and other stakeholders regarding their AE reporting practices. The FDA regularly communicates to sponsors the importance of reducing uninformative safety reports. OHOP has provided sponsors with educational AE case studies. It has also issued letters requesting that companies with more than three active INDs investigating the same drug only submit AE reports to the IND under which the AE occurred and to the IND with the lowest number of reports.[20] Similarly, researchers and research sites are capable of providing feedback on the importance of sponsors adopting best practices. Sponsors' receptiveness to this feedback may motivate adoption of best practices.

In addition, it is imperative that CROs modify their procedures in response to feedback from stakeholders in the AE reporting process because, as noted above, sponsors often charge CROs with managing their AE reporting process. CROs may unintentionally add to the burden on investigators and sites.

Recommendation 1.c. Sponsors and CROs should be transparent about their AE reporting practices. Sponsors and CROs should make their AE reporting practices more transparent at the outset of trials. Investigators and research sites could then consider these practices when deciding whether to open a trial. Moreover, improving sponsor and CRO transparency may actually incentivize them to streamline their practices, because they will want to demonstrate that they are optimally protecting research participants' safety and operating efficiently. The fear of revealing trade secrets or losing a competitive advantage may undermine this strategy.

Recommendation 2. Researchers and Research Sites Should Adopt Best Practices for Reporting AEs to Sponsors

Investigators play a critical role in the AE reporting process by observing research subjects' responses to investigational treatments. They are required to report all serious AEs to sponsors and to include an assessment of causality. There is evidence, however, that investigators are not reporting high-quality or complete information in safety reports and that they struggle with attribution.[21-24]

Recommendation 2.a. Clinical trials educational programs for investigators should emphasize the importance of reporting serious AEs accurately and completely. AE training has been requested within the NCI Cooperative Groups by investigators and research staff,[25] as well as being identified as a top priority by ASCO members through the Best Practices in Cancer Clinical Trials Initiative.[5] Evidence from the Children's Oncology Group showed that professional development webinars on AE reporting are well attended and inform research professionals' behavior.[25] To meet investigators' ongoing AE educational needs, existing clinical trials educational programs (eg, Good Clinical Practice training and professional organizations' educational programs) should emphasize the importance of proper AE reporting. Specifically, this training should focus on the FDA's criteria for expedited reporting, highlighting case-based examples and providing template language for attribution justification. These programs should emphasize that investigators should not classify AEs as reasonably related to the drug just because they cannot rule out a causal relationship. Investigators should also be made aware that their causality assessments (or lack of a causality assessment) might drive expedited reporting to regulatory agencies other than the FDA, depending on local requirements. One potential obstacle to this recommendation is the burden of multiple training requirements on investigators.

Recommendation 2.b. Sponsors should recognize and promote the use of centralized training for investigators. Sponsors and CROs often have training programs specific to their organization or even to individual trials within their portfolio; this undermines the goals of efficiency and effectiveness. A centralized approach to investigator training that is recognized by all sponsors could eliminate the potential obstacle described in recommendation 2.a of multiple training requirements. This recommendation is aligned with earlier recommendations from the ASCO-AACI Best Practices in Cancer Clinical Trials Initiative, which recognized the need to centralize investigator training.[4] Moreover, there are existing efforts to consolidate investigator and site qualifications, such as TransCelerate BioPharma's Investigator Registry,[26] which can capture investigators' completed training and may reduce the likelihood of sponsors requiring redundant training. Stakeholder buy-in will be critical for this approach to be effective.

Recommendation 2.c. Research sites should adopt and adhere to standard operating procedures for AE reporting that are based on the 2010 FDA Final Rule. Researchers and research sites' participation in the AE reporting process could be improved through the development of SOPs. At the workshop, representatives from multiple institutions noted that their research sites have SOPs in place to prevent uninformative AE reports from being reported to their institutional review boards (IRBs). However, SOPs could be further developed to improve the detection, evaluation, and reporting of AEs during cancer clinical trials. For example, two studies by Belknap and colleagues[27,28] identified methods for improving AE reporting to IRBs via structured case abstraction forms that prompt entry of the data necessary to evaluate an event. The challenge is that standardized SOPs do not currently exist; however, professional organizations could help to develop and disseminate model SOPs that sites could adopt. For this strategy to be effective,

it will be critical that sponsors and CROs not add reporting requirements beyond those in the 2010 Final Rule.

Recommendation 3. International Regulatory Agencies Should Harmonize the Regulations for AE Reporting

The FDA's rules for AE reporting and the International Conference on Harmonization (ICH) E2A Guidelines that are followed by other countries have several important differences. The most substantial difference is regarding the party responsible for making causality determinations. Under FDA rules, the sponsor determines the causality of an AE; under the ICH E2A, the causality of AEs is determined by either the investigator or the sponsor.[29] This difference substantially affects which and how many AEs are sent to the regulatory agencies and participating investigators.

Sponsors consistently indicate that lack of legal harmonization around causality assessments undermines compliance with the FDA's 2010 Final Rule.[3] Representatives at the workshop noted that differential reporting to the FDA and other international regulatory authorities is technically possible either with an off-the-shelf safety system or manually. Some companies have systems in place to send the FDA only those expedited IND safety reports that they have confirmed meet the standards in the 2010 Final Rule (ie, serious, unexpected, positive causality from the sponsor), whereas they send the rest of the world safety reports on the basis of local and regional requirements (eg, serious, unexpected, positive causality from either the investigator or the sponsor). However, the cost required to support this process may be prohibitive for some stakeholders.

Recommendation 3.a. All stakeholders worldwide should support international regulatory harmonization. Changing the regulations is a time-consuming and challenging process, especially country by country. Thus, to the extent possible, the FDA and other regulatory agencies should identify areas where harmonization is possible through clearer interpretation of the rules and uniform guidance to sponsors and investigators. However, it is likely that international regulators will need to modify their rules to achieve full harmonization with the FDA's requirements. Investigators should work with patient advocates, sponsors, and other stakeholders to advocate for these changes.

Recommendation 4. All Stakeholders Should Use Modern, Digital Technology to Report AEs

Many sponsors collect safety data from investigators through sponsor-specific electronic portals. The NCI Cancer Therapy Evaluation Program is also in the process of creating a technology platform for managing electronic submission of AE data from its trials. Stakeholders' use of technology, however, is not optimal. A 2014 CTTI survey of 201 investigators and study staff found that, although the majority of respondents receive IND safety reports from sponsors through electronic portals, approximately 50% of investigators and 44% of staff find the portals difficult to use.[30] Respondents indicated that problems relate to remembering passwords for numerous individual sponsor sites, navigating the sites, ensuring compatible software, preventing log-on issues due to staff turnover, limiting excessive e-mail notifications, and downloading reports in an efficient manner.

Recommendation 4.a. A neutral third party should develop a central electronic portal for reporting AEs. A neutral third party, such as a nonprofit organization formed by an industry consortium or a public-private partnership, should create a globally available, central electronic portal that enables users to report and access AE data relevant to all trials in which they participate. This would provide investigators with context to inform clinical judgments regarding attribution of AEs, as well as facilitate regulators, sponsors, and IRBs identification of important safety signals. In addition, a central portal would address some of the limitations of sponsor-specific reporting systems that the CTTI survey identified by creating a single login password, standardizing visualization across trials and sponsors, and eliminating software compatibility issues. A potential source of funding for this project is subscription fees from the sponsors that use the system. Sponsors may be motivated to participate in this system because of the potential cost savings of using a centralized approach to safety reporting.

For the central portal to reach its full potential, it will be critical that it is coordinated with the FDA and international regulatory agencies' efforts to collect electronic safety data. For example, the FDA recently launched a pilot program that is evaluating the feasibility of allowing sponsors to electronically submit their safety information rather than provide paper or PDF Medwatch forms (FDA form 3500).[31] The pilot program relies on the FDA's Adverse Events Reporting System, which was developed based on the ICH E2B standards for the postmarket safety surveillance of drugs and biologics. Moving forward, it will be important to develop a mechanism for the FDA's Adverse Events Reporting System to transmit data directly to the central portal or to ensure that the FDA can access all of the necessary safety data within the central portal database. It will also be critical that other stakeholders have access to aggregate safety data in the central portal, including IRBs, investigators, sponsors, and regulators. Potential challenges to developing central portal include stakeholder buy-in, governance, and the cost of development.

In conclusion, current safety reporting practices place a substantial burden on the FDA, researchers, and research sites, while failing to optimize patient safety; efforts to streamline AE reporting have not solved the problem. Nevertheless, improvements can be made, as demonstrated by the companies that have fully implemented the 2010 Final Rule. Certain companies have reported methods for dramatically reducing the number of AE reports and increasing their impact. Future efforts to streamline the AE reporting process should focus on encouraging all sponsors and CROs to adopt best practices in implementing the 2010 Final Rule. Investigator education that empowers investigators only to report AEs that meet the requirements in the 2010 Final Rule will also be crucial to improving the process. In addition, developing SOPs for research sites, harmonizing legal requirements, and creating a centralized electronic system for collecting and disseminating aggregate safety data may further improve AE reporting. Altogether, these recommendations would improve safety for research participants and provide better data from clinical trials.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

AUTHOR CONTRIBUTIONS

Administrative support: Laura A. Levit
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