

missing so many opportunities to turn heartbreaking tragedy into bittersweet success.

Disclosure forms provided by the author are available at NEJM.org.

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The FDA Sentinel Initiative — An Evolving National Resource

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The Food and Drug Administration (FDA) Sentinel Initiative,¹ which was launched in 2008, has matured from a pilot program designed to assess potential drug-safety signals in insurance claims into a core component of the agency's evolving safety surveillance system. Sentinel is a flexible and robust program that provides evidence on the effects of medical products while protecting patient privacy; it uses a distributed data network that contains curated electronic health data covering more than 100 million people. The FDA regularly conducts safety analyses of the billions of hospital stays, outpatient visits, and pharmaceutical dispensings included in the Sentinel System.

To develop Sentinel, the FDA partnered with more than 200 health system leaders, pharmacoepidemiologists, clinicians, data scientists, patient representatives, and other experts from 31 health plans and academic organizations. Early on, the group focused on privacy and governance issues in order to support broad participation while addressing concerns related to confidentiality and proprietary information. The lead team then designed and built a

secure querying system, created a very large rigorously curated and updated distributed health information data set, and developed tools permitting rapid, customized analysis.

Distributed data systems, in which data partners maintain physical and operational control over their data, provide a high level of protection for the privacy and security of patients' health information. Each data partner formats a copy of its data according to the specifications of the Sentinel Common Data Model and keeps the transformed data behind its existing firewalls. Neither the FDA nor the Sentinel Operations Center takes possession of these data sets; instead, questions in the form of executable computer programs are sent to each data partner. The partner returns only the results, which typically contain information such as counts of exposed people and outcomes of interest. Sentinel methodologists have developed and implemented techniques for performing sophisticated analyses such as propensity score matching and self-controlled analyses in a distributed environment. Scientists at each partner system also participate in this process, pro-

viding guidance on the best use of their data. Although data partners have chosen to respond to nearly all questions sent to them, their ability to opt out of specific queries remains an important contributor to their willingness to participate in the program.

Administrative claims data are the foundation of the Sentinel infrastructure because they are the most reliable and readily available source of complete longitudinal information about medication dispensing and medically attended events, regardless of where care is provided. The system is also able to link to registries and incorporate certain electronic health record data. In addition, when a specific analysis requires data available only in a medical chart, data partners are authorized to request this information from providers.

Sentinel data have informed many regulatory decisions made by the Center for Drug Evaluation and Research and, in the past 2 years, have eliminated the need for postmarketing studies on nine potential safety issues associated with five products (e.g., ustekinumab and serious infections). Such postmarketing studies typically require years to design and com-

plete, each at a cost of millions of dollars. The FDA has also used the Sentinel System to better understand patterns of use of opioids and other medical products, including whether medical products are used in accordance with approved indications and how they are used during pregnancy, to quantify the rate of medication errors, and to assess the effects of medical countermeasures used in public health emergencies. All drug-evaluation protocols are posted on the Sentinel Initiative public website for comment, as are completed analyses. Starting this year, fully executable programs and standardized specifications for all analyses will be posted, which will enable replication in other environments.^{2,3}

The FDA has used Sentinel's capabilities to create a parallel program, FDA-Catalyst, that allows direct outreach, in collaboration with participating data partners, to providers and health plan members. The program has enabled researchers to conduct pragmatic clinical trials embedded in real-world delivery systems. The IMPACT-AFib study, for example, is an 80,000-person, individually randomized clinical trial testing the effect of educational mailings to health plan members with atrial fibrillation who are at high risk for stroke and who appear not to be receiving oral anticoagulation and to their providers, who can encourage and initiate treatment if it is indicated (ClinicalTrials.gov number, NCT03259373). The Sentinel infrastructure is used to identify eligible health plan members and assess key outcomes, such as initiation and continued use of anticoagulants and hospitalizations for stroke, transient ischemic attack, and bleeding.

Just as the Sentinel Initiative looks very different today than it looked 5 years ago, in 5 to 10 years the system will have improved capabilities and will use new data sources and methods. Experience operating the Active Risk Identification and Analysis system, which consists of modular programs that apply sophisticated epidemiologic methods to distributed data sets, has illuminated opportunities for enhancement. Examples of such approaches include distributed regression methods that preserve privacy and enable analysis of individual patients' data when they are distributed throughout multiple organizations, as well as adoption of machine learning, natural language processing, and other technologies that enable improved use of electronic health records or other sources of real-world data. The Sentinel Initiative can become a critical component of the FDA's implementation of its mandates under the 21st Century Cures Act by providing data and expertise to support the incorporation of real-world data into regulatory decision making in other areas in addition to safety assessments.⁴ To complement existing Sentinel capabilities, the FDA is also building separate programs tailored to the distinct data needs of its Center for Biologics Evaluation and Research and its Center for Devices and Radiological Health.

The Sentinel Initiative has also made substantial progress toward fulfilling the FDA goal for the system to become a national resource for evidence development and a cornerstone of a learning health care system. The Initiative's partner organizations now use their data, methods, and tools to work with the Reagan-Udall Foundation Innovation in Medical Evi-

dence Development and Surveillance program, the National Institutes of Health Health Care Systems Research Collaboratory Distributed Research Network, the Patient-Centered Outcomes Research Institute's PCORnet, and the Biologics and Biosimilars Collective Intelligence Consortium. Sentinel's tools and data structures have also been used by manufacturers of products regulated by the FDA, and they have been adopted by the Canadian Network for Observational Drug Effect Studies program, enabling regulatory agencies to execute a single query in both national systems. Additional opportunities exist for leveraging the FDA investment in the Sentinel System, including broadening engagement with the public health community to support chronic and infectious disease surveillance activities by federal, state, and local public health agencies. Opportunities also exist for supporting new quality-improvement programs for delivery systems and payer organizations.

As the Sentinel program approaches its 10th anniversary, it has become instrumental in advancing the use of distributed health data systems. Partners of the FDA and Sentinel are committed to continuing to harness the system to advance knowledge for the common good.

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Sit Back and Listen — The Relevance of Patients' Stories to Trauma-Informed Care

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Long before standardized, data-based templates began to dictate the patient history, a teenager from Sudan walked into my pediatric practice in Philadelphia. He suffered from chronic headaches that defied all attempts at diagnosis. I ruled out sinusitis and migraines and the exotic parasites I remembered from medical school. I asked about stress and depression. He insisted he was fine.

Over time, as we tested a variety of medications and dietary changes, he gradually revealed the details of his journey. He explained that when he was a small boy, rebel soldiers burned his village. His family was massacred. He fled to the bushes with scores of other boys, and together they endured dire conditions as they walked for more than a thousand miles through the wilderness. After losing many boys to starvation and illness, the ones who survived found their way to a series of refugee camps, where they were dubbed the “Lost Boys of Sudan.” From there, my patient was eventually resettled in the United States, in an area near my practice.

The more I got to know him, the more grounded I found him to be. He described feeling responsible for a younger cousin he had left behind in the refugee camp. He talked about his friends, other Lost Boys who were reset-

ting in cities and towns around the United States. He studied geometry and history and chemistry at his new American high school. At one point I asked about a bruise on his face, and he explained that he had had to restrain an intoxicated acquaintance to keep him from fighting. But alcohol was no excuse for unruly behavior, he said. Because “you choose to drink the alcohol — it



does not drink you.” He was kinder and wiser than most adults I have ever known.

One day after I had cared for him for several years, he came in with worsening headaches. I asked the usual questions about sleep and hydration and was about to suggest additional tests when he said there was one more thing. His mother had been found alive. A relief worker from his village had sent him a photo in which she appeared emaciated, almost lifeless, and living in squalid conditions. “Like an animal,” he said.

He was determined to go back to Sudan to find her. But he knew this wasn't possible. And his helplessness in the face of her pain, he thought, might be why his head was hurting.

At a moment such as this one, everything outside the exam room ceases to exist. We shift from a pressured focus on time management and efficient documentation to a quieter mode of doctoring.

As we absorb the stories that shape our patients' lives, we feel their full impact.

If there is one thing I have learned over 22 years of practicing pediatrics in an under-resourced urban environment, it is that patients reveal their most personal and painful life experiences when we build trusting relationships and encourage open dialogue. The more we understand about the long-term effects of toxic stress¹ due to adverse childhood experiences,² the more important it becomes for us to absorb these stories. They form the crux of trauma-informed care.

But how can we encourage open dialogue in today's health care climate? Doctor-patient interactions are increasingly scripted. The patient history, once a blank slate on which we could record the individual narrative as it evolved, is now a minefield of standardized, quantifiable click-boxes and questionnaires that dictate the