

FDA Sentinel Initiative Strategic Review

The Sentinel Initiative: Review of the First Three Years

With passage of the Food and Drug Administration Amendments Act of 2007 (FDAAA), Congress mandated that the U.S. Food and Drug Administration (FDA) develop a system for postmarket risk identification and analysis using existing electronic health data. In response to this charge, FDA launched the Sentinel Initiative in 2008. Since that time, FDA has made significant progress in developing a system for conducting active surveillance of medical products and is on track to exceed its congressional mandate to be able to access data from 100 million patients by July 2012. The Sentinel Initiative currently comprises four major activities:

- **Mini-Sentinel:** This pilot project, led by Harvard Pilgrim Health Care Institute, is developing the infrastructure, methods, governance, and other capabilities needed for the fully operational Sentinel System to conduct active medical product safety surveillance. Mini-Sentinel uses a distributed data system and common data model, which reduces security and privacy concerns by keeping data behind data partner firewalls and takes advantage of data partner expertise, which can help to ensure proper use and interpretation of the data. At present, Mini-Sentinel has three options for utilizing the data within this pilot: via pre-tabulated summary tables, reusable modular SAS programs, and custom SAS programs. The former two approaches allow for rapid queries. Summary tables can provide prevalence counts of enrollment, diagnoses, procedures, and drug utilization. Modular SAS programs are particularly useful because they can yield results within days or weeks. These programs produce counts, and in some cases rates, for specified age, sex, and calendar time strata, but do not currently adjust for confounding factors. Developing custom SAS programs often requires more time, but this approach supports more in-depth assessments and allows for controls of other potential confounders. Earlier this year, Mini-Sentinel initiated programs to explore the relationship between myocardial infarction and oral hypoglycemics, intussusception and rotavirus vaccines, and venous thromboembolism and human papillomavirus vaccine.
- **The Observational Medical Outcomes Partnership (OMOP):** OMOP has established a comprehensive research program to empirically evaluate the performance of methods, characterize disparate observational databases, and establish a shared resource of tools and capabilities that enable and foster open innovation within the safety science research community. Since its launch, OMOP has demonstrated the feasibility of establishing both a centralized data resource and a distributed data network to facilitate the development of a systematic and automated risk identification and analysis system. This includes the successful development and implementation of a common framework (data model and standardized terminology) that enables analysis across both administrative claims and electronic health records and a multi-stakeholder governance structure to oversee OMOP. OMOP has completed its originally defined set of research experiments to empirically evaluate the performance of alternative methods on its ability to identify true associations between drugs and outcomes. To conduct these experiments, OMOP established a data community (central and distributed) of 10 data partners containing both administrative claims and electronic health records and covering over 200 million lives of patient-level data. OMOP also engaged the community of methods developers to implement 15 alternative analytic approaches for estimating the strength of association between medical product exposure and outcome occurrence. OMOP promotes transparency by making all information public domain as quickly as possible, which creates a broader research community. Today, OMOP is working to evaluate method performance against

a larger array of drug-outcome test cases and systematic investigation of both real and simulated datasets.

- **Federal Partners Collaboration:** This pilot has established a distributed system to conduct safety assessments among several federal agencies and departments, including the Centers for Medicare & Medicaid Services, the Department of Veterans Affairs, and the Department of Defense. Rather than using a common data model, each data partner leaves their data in its native structure and develops a shared protocol collaboratively with agreed upon definitions. Since initiation of this pilot, federal partners have developed an understanding of the differences in data characteristics and an infrastructure that allows the agencies to work within their current data and analytic frameworks.
- **Brookings' convening activities:** Under a cooperative agreement with FDA, the Engelberg Center for Health Care Reform at the Brookings Institution convenes a number of meetings to engage stakeholders in both technical and policy discussions related to active surveillance of medical products and the Sentinel Initiative. In addition to bringing together the expertise of diverse stakeholders, these meetings also serve as an important vehicle for communicating updates on the Sentinel Initiative to the public.

Each of these Sentinel Initiative activities has contributed to developing a set of tools to support exploration of safety signals, and, given the success thus far, it will be important to consider next steps to sustain this upward trajectory towards building a postmarket active surveillance system. On September 26 and 27, the Engelberg Center for Health Care Reform at Brookings convened the "FDA Sentinel Initiative Strategic Review," bringing together a diverse group of stakeholder representatives to reflect upon Sentinel's progress to date and consider its future direction as a sustainable resource. This document highlights major points of discussion from the workshop.

Priorities for Continued Progress

While the Sentinel Initiative has made significant strides during its first three years, continued success will require maintaining and expanding stakeholder involvement, developing policies to appropriately communicate Sentinel's capabilities and results to different stakeholder groups, and improving confidence in methods. Each of these priorities, and potential next steps to address them, is described in greater detail below.

Maintaining and Expanding Stakeholder Involvement

The Sentinel Initiative relies on a range of different stakeholder groups to provide strategic and technical expertise, access to data, and regular input on planned activities and approaches. As Sentinel develops further, maintaining and expanding this broad-based stakeholder support will be imperative. Representatives at the meeting suggested some opportunities in this area.

- Medical product developers indicated that because of the pharmacoepidemiology and pharmacovigilance expertise, familiarity with the product, and experience with risk communication of their staff, they have much to contribute to FDA's active surveillance activities. Medical product developers voiced interest in being involved in the design of assessments and obtaining results derived from the Sentinel System so that they can help patients and providers understand those results. They also stated that being notified of upcoming assessments on their products would allow them to better prepare to address patient and provider questions and concerns.
- While representatives of patient and consumer advocacy organizations have participated in several meetings convened for the Sentinel Initiative, some believe there is an opportunity for even greater patient involvement. In particular, patients and consumers may be able to provide valuable input in areas such as the most important and meaningful health outcomes to evaluate and strategies to effectively communicate results.
- Data and analytic partners have been active participants in the Mini-Sentinel pilot (e.g., leading specific FDA-task orders, facilitating access to data, providing methodological expertise, analytic support for queries, and formatting and quality-checking data). To ensure awareness throughout each data partner organization, participants suggested providing recognition for data partners' role and contributions (e.g., via letters to data partner executive leadership, annual reports that

highlight achievements of the pilot) and continuing to meaningfully incorporate their expertise as active research partners rather than merely passive data holders.

Next steps to maintain and expand stakeholder involvement include developing policies for appropriate involvement of medical product developers, developing channels to substantively engage patients and consumers, and continuing to preserve data partner participation as vital partners in the safety surveillance process.

Develop Communication Policies

As Mini-Sentinel develops further and launches an increasing number of assessments, it will likely capture more public attention. FDA has repeatedly emphasized that the Sentinel System is only “one tool in the Agency’s tool box,” and that any data derived from Sentinel will be considered within the context of all other available data. Yet, because of the novelty of this system, it will be important that clear communications strategies tailored to several different stakeholder audiences that promote understanding and appropriately manage expectations be developed. Next steps include developing clear communication messages for each group that help them to understand use and limitations of Sentinel and equip them with tools to support informed health care decision-making.

Improve Methods to Increase Confidence in Results

Stakeholder support for this active surveillance effort will hinge on confidence in the results generated through the Sentinel System. One important way to build this confidence is through a better understanding of the data, its limitations, and appropriate uses and the most appropriate analytic methods. While this is broadly recognized as a priority, work still needs to be done before our understanding of the data and appropriate methods is adequate. At present, there is insufficient convergence around what methods are most appropriate for certain types of surveillance monitoring. In the absence of evidence to inform proper methods selection, different methods may be applied to answer the same question but return divergent results that are difficult to interpret.

Launching a multi-stakeholder effort to create a sustainable national safety science methods and training development program is an important first step to address this priority. Components of a successful and sustainable program include developing and overseeing a national strategy, building a methods research and development lab, and administering a training fellowship for future safety scientists. The strategy can include plans for how to set priorities, an action plan and timeline, a pathway to integrate with parallel research efforts, periodic updates on what methods should be used in various situations, and a mechanism to evaluate the program’s outcomes. To date, a hallmark of Mini-Sentinel’s progress has been extremely close coordination in developing the research agenda to meet the needs of the pilot and implementation of those methods. Similarly, creating strong operational links between this safety science methods development program and the operational arm of the Sentinel System can emulate Mini-Sentinel’s success. Developing a national strategy for methods development can also increase efficiency by consolidating various methods research and development initiatives that currently occur as separate efforts. Ultimately, this effort should aim to increase confidence in methods selection and use of the data through a convergence of the most reliable and appropriate methods based upon assessment characteristics. Next steps include creating a multi-stakeholder workgroup to develop a proposed work plan and timeline, and identifying an organization, outside of FDA, to oversee the implementation of the various components of this national safety science methods and training development strategy.

Creating a Sustainable Resource for Evidence Development

In addition to addressing the priorities identified above, it is necessary for the safety science community to begin long-term planning to ensure financial sustainability of the groundwork that has been laid through FDA’s initial investments in the Sentinel Initiative. It is also important for the community to consider ways to expand the existing infrastructure and tools to enable broader application beyond safety surveillance. To date, FDA has provided funding to support Mini-Sentinel, the Federal Partners Collaboration, and Brookings’ convening activities. While FDA intends to continue to support these activities to the fullest extent that resources permit, realizing the full potential of electronic health care data will require external support for broader methods research and development and related training efforts and use of the distributed data system for non-FDA medical product safety queries and other secondary purposes (e.g., patient-centered outcomes research, quality measurement). Meeting participants considered a potential

three-step plan to transform the resources developed under the Sentinel Initiative into a sustainable entity that does not rely solely on FDA funding.

Public-Private Partnership to Support Postmarket Safety Science Research

Public-private partnership is a potential strategy to sustainably oversee the national safety science method development strategy described above. The purpose of such a partnership would be to support and expand upon the active surveillance methods that have already been developed by the investigators of the Mini-Sentinel Methods Core and OMOP for FDA's safety assessments. To ensure an efficient and streamlined process for methods research and development, the partnership, as an independent entity, can consolidate these separate research efforts while maintaining strong operational ties to the Sentinel System to ensure that Sentinel's methodological needs are met. The partnership could also create and administer a training fellowship program that includes opportunities for fellows to rotate through different organizations. Determining a suitable organization to house this partnership will be important, and some meeting participants proposed the Reagan-Udall Foundation. However, regardless of where the partnership is housed, a helpful next step for the safety science community is to work together to draft a scope of work, develop a resourcing model and timetable, draft governance policies, propose membership of a governance board and a scientific advisory board, and develop a plan for the training fellowship.

Creating an Opportunity for Non-FDA Users to Access the Tools and Distributed Data System Established for Mini-Sentinel to Conduct Post-Market Safety Studies

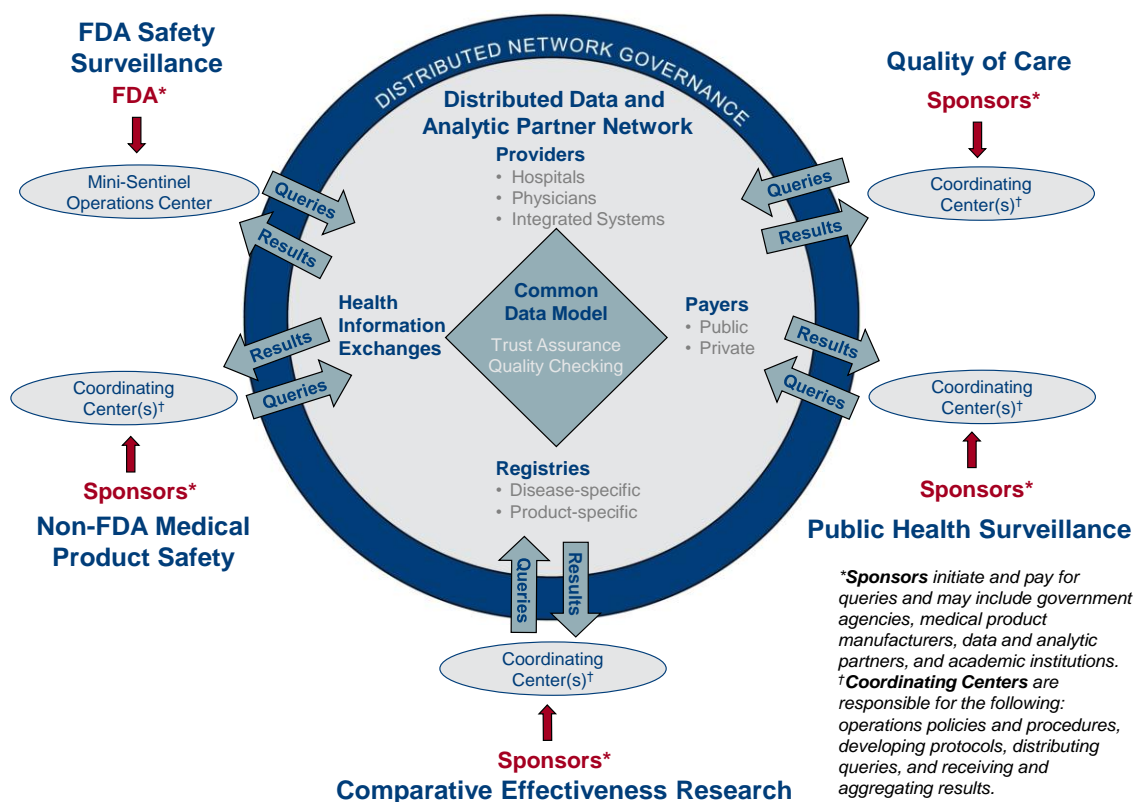
A logical way to expand access to the tools and distributed data system that were established under the Sentinel Initiative is to allow organizations such as medical product developers, academic institutions, or other federal agencies to conduct their own medical product safety studies (e.g., phase IV studies required by FDA). During the meeting, several participants expressed an interest in using these tools for such a purpose. However, it is important to recognize that the network of partners currently contributing data to the Mini-Sentinel distributed data system have only agreed to provide access to data for FDA's safety surveillance uses in support of public health. Further, under Mini-Sentinel's governance policies, data partners have the opportunity to opt in or out of any FDA-initiated query.

Although FDA has stated that it is eager for others to leverage the tools and infrastructure supporting Sentinel's distributed data system, actual use of the distributed data system by non-FDA users would require addressing several key governance and policy issues. First, it would require creating a separate mechanism from FDA's Sentinel System for non-FDA stakeholders to use the distributed data system. Second, this new mechanism would necessitate development of separate governance. This governance structure would need to be developed and overseen by a third party; this third party could potentially be the same public-private partnership that would support methods research described above. Governance policies would need to address security and privacy of data, scientific oversight, guidelines for participation and access, procedures for expanding or modifying the tools and distributed data system, protocol development, transparency and publication, and prioritization of questions and quality control. Meeting participants emphasized the importance of close collaboration with data partners as these governance policies are established. Finally, a resourcing model must be identified to support broader use. Participants proposed several potential models, all of which warrant further consideration and would benefit from broader stakeholder input.

Expanded Use of the Distributed Data Infrastructure and System for Other Purposes

As FDA, via the Sentinel Initiative, has been establishing the infrastructure and capabilities for safety surveillance described above, other initiatives have simultaneously begun exploring the value of using electronic health care data for other uses. Examples of other initiatives include the Office of the National Coordinator for Health Information Technology's Query Health and the Department of Health and Human Services' Multi-Payer Claims Database, which are developing similar tools to those developed for Sentinel for other uses than medical product safety surveillance. These initiatives are in early stages of development and therefore may benefit from leveraging some of the infrastructure and tools developed for the Sentinel Initiative. Use of a common data model, such as the one created for Mini-Sentinel, is a particularly powerful tool that could unify multiple concurrent initiatives. If these initiatives could work together to agree upon a single common data model, data partners would be able to participate in multiple initiatives with minimal incremental effort, given that only a single data transformation would be

required (i.e., into the common data model format). Broad use of a single common data model would also enable efficient access to the distributed data system for other uses beyond the initiatives mentioned above. Once again, enabling access to the distributed data system established for Sentinel for these types of uses would require the establishment of additional portals and corresponding governance policies as outlined in the previous section. Perhaps the most efficient mechanism for expanding access for multiple uses beyond safety science involves creating a single entity that would be responsible for governing the entire distributed data system as depicted below.



Stakeholder Groups with a Potential Interest in Supporting these Efforts

Meeting participants identified at least two broad stakeholder groups that might see value in supporting the public-private partnership and expanded use activities described above. Medical product developers would have several potential benefits. First, as medical product developers invest in methods and training to support safety science through the proposed public-private partnership, the entire enterprise will be strengthened. Second, participation in the public-private partnership would provide medical product developers opportunities to participate in pharmacovigilance and pharmacoepidemiology fellowship programs, thereby enriching their internal expertise. Lastly, medical product developers would have access to additional data, methods, and tools to augment their current capabilities to conduct observational studies to fulfill phase IV requirements and non-FDA requested studies.

Data partners are another stakeholder group that may benefit from participation in and support for these activities. As described above, continuing to engage them in the Sentinel Initiative is vital for its success. Development of a public-private partnership and expanded use of the distributed data set will also rely on data partner collaboration. While data partners are interested in participating in secondary uses of data, resource constraints may prevent some data partners from doing so given an increasing number of data requests that each require a different data format. If a single common data model is adopted to facilitate

expanded access to the distributed data system, some data partners may view this as reducing the burden of participating in other initiatives and allowing broader participation in these types of population-level public health activities. Participation in the public-private partnership could provide data partners with an opportunity to further strengthen their own methodologic and analytic capabilities.

Conclusion

Through the Sentinel Initiative, FDA has made strides in creating a valuable tool to advance FDA's medical product safety monitoring capabilities. FDA's investment in this system has helped to yield a variety of methods and tools, and a distributed data system, which will prove valuable not only for addressing FDA's safety questions but may also have potential utility beyond the field of medical product safety. Realizing this potential will require active engagement, regular input, and additional investment from a range of stakeholders, including FDA.