BUILDING A NATIONAL RESOURCE FOR EVIDENCE GENERATION

Exploring How Sentinel Infrastructure Could Generate Real-World Evidence on PCSK9 Inhibitors

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Meeting Summary

The Robert J. Margolis Center for Health Policy at Duke University, under a cooperative agreement with the U.S. Food and Drug Administration (FDA), is exploring the potential for broader use of the Sentinel System’s data infrastructure and partnerships. The Sentinel System is designed to monitor the safety of FDA-regulated medical products, but it also has the potential for its data infrastructure to be used for quick and efficient development of real-world evidence. Further, the FDA’s vision is to extend the Sentinel System, and thereby leverage its investment in the System, by having it serve as a national resource that develops efficient real-world evidence to address critical questions of importance to public health and multiple health system stakeholders.

There is a growing need for more evidence on what services and medical products work best and for whom, with key stakeholders – such as providers, patients, health systems, and payers – requiring more evidence. These stakeholders’ questions could potentially be answered at a population level with the Sentinel System’s data infrastructure, which, in addition to providing valuable data on safety, could generate key insights into the effectiveness and value of these treatments, when used in real-world practice settings to decide what therapy might work for a given patient.

Through exploratory discussions with stakeholders, Duke-Margolis has identified the cholesterol-lowering anti-PCSK9 monoclonal antibodies, or PCSK9 inhibitors, as a promising use case to explore the feasibility of generating real-world evidence using the Sentinel System data infrastructure. Specifically, the goal would be to answer high-priority questions that could not otherwise be answered without this unique data resource. PCSK9s were identified as a good test case based on extensive stakeholder discussions leading up to the workshop; stakeholders shared their interest in more PCSK9 evidence in part because of their high cost relative to existing lipid-lowering treatments such as statins and current uncertainties on their utilization and impact on patient outcomes in real-world practice settings. PCSK9 inhibitors are a relatively new class of drugs, with two products approved in 2015 and additional products in late-stage clinical development. Given the new nature of this class, there remain unanswered questions where real-world evidence is needed.

This meeting summary comprises the broad themes and specific commentary discussed by the participants at the workshop.

Meeting Details
The Duke-Margolis Center convened a workshop with representatives of the FDA, patient representatives, payers, integrated health systems, non-profit research institutions, cardiovascular specialists, and data analytics professionals to understand the challenges and opportunities to developing a Sentinel System study for PCSK9 inhibitors.
The first day of the two-day workshop included a larger group assessing the feasibility of exploring high-priority PCSK9 inhibitor research using the Sentinel System infrastructure and a smaller group on the second day exploring the detailed practical considerations including key operational issues, administrative needs, and the value proposition for data partners to participate.

The specific objectives for the workshop included the following:

- Explore how real-world evidence could be developed through the Sentinel data infrastructure, using PCSK9 inhibitors as a test case to orient the discussion.
- Identify the gaps in what we know about the PCSK9 class of drugs, especially the evidence on how these drugs are being used in real-world environments and their outcomes.
- Describe how to generate evidence in those gaps areas, especially leveraging the Sentinel system’s data infrastructure.
- Outline how to link with other initiatives, such as other data sources, payer-led initiatives, and research projects.

Following on this project, the Duke-Margolis will engage with stakeholders to explore a pilot project that could generate needed evidence about this new class of drugs.

Important Evidence Gaps for PCSK9 Inhibitors: Key Perspectives

A number of high priority evidence gaps for PCSK9 inhibitors were highlighted during the workshop. Unsurprisingly, different stakeholders bring different views on the specific gaps that are highest priority. Regardless of the stakeholder perspective, there was general agreement that more research is needed. This section outlines the evidence gaps that were discussed during the meeting, and the following section addresses which of these gaps could be feasibly filled using the Sentinel infrastructure.

Several attendees emphasized the need to characterize the population receiving PCSK9 therapy, including utilization trends alongside statin use and other potentially complementary cardiovascular disease (CVD) or atherosclerotic disease (ASCVD) interventions. Given how PCSK9s are currently administered as a subcutaneous injectable, some participants noted the need for better evidence on adherence rates. Beyond utilization and population characterization, there may be opportunities to identify effectiveness in specific sub-populations (which may not have been included in the clinical trials to date) or whether there are predictors of greater or less benefit from the therapy. This real world evidence would supplement clinical trial results, such as the FOURIER outcomes trial.

One common theme was the importance and challenge of generating evidence for the questions patients have about the treatment, from patient experience with these therapies (including side effects) to the health outcomes most meaningful to patients. For example, PCSK9 inhibitors are currently indicated as an adjunct to maximally tolerated statin therapy, but there is no broad consensus on what “maximally tolerated” means. Further, several participants noted that statin tolerance (and intolerance) is poorly understood, and different patients will have different perspectives on statin (in)tolerance. Other participants indicated that an ideal evaluation will include measures and outcomes that patients would find useful for their decision making, and further work is needed to construct such measures from currently available data.

Several participants emphasized the value in having a standing resource that can quickly quantify utilization trends along with short term effectiveness once treatments are approved and enter the market. This analysis would build on the summary tables of utilization for new molecular entities using the Sentinel System data.
High Priority Questions to Potentially Address through the Sentinel System’s Capabilities

During workshop discussions, the participants highlighted a number of high priority gaps where more evidence is needed and considered how this evidence could be generated using Sentinel System’s unique capabilities and data infrastructure. The Sentinel System could be a valuable resource for evidence generation given its unique value as a source of claims data, analytic tools, and research partnerships, and with more than 300 million person-years of curated data to rapidly scale analyses through a Common Data Model (CDM).¹

The participants examined high priority research questions in light of the Sentinel System’s capability. The research questions generally fell into two categories: characterizing the treated population to identify trends in utilization, and understanding the overall effectiveness and outcomes of PCSK9 inhibitors.

The Sentinel System is well positioned to address the first category of questions to establish a baseline of utilization and population characteristics to follow over time. This will allow for payers to better understand the usage of these drugs in their covered populations, and evaluate how prescribing and use relate to indications and clinical guidelines. Specific factors to track could include:

- Characteristics of patient population (e.g. age, sex, race/ethnicity, prior diagnoses).
- Characteristics of the treatments (e.g. date of prescription, duration of therapy, prior cholesterol-lowering treatments, dosages, length of enrollment in the health plan).
- Characteristics of the data (e.g. completeness and missingness).

Although PCSK9s would be a focal point for the initial analysis, workshop participants also acknowledged more evidence is needed for other cholesterol treatments. These treatments are often taken in combination with each other, including treatments such as statins, which are a first-line therapy for lowering cholesterol, and ezetimibe. In addition to existing treatments, analyses could prepare to incorporate medical products in advanced development that are expected to receive marketing approval over the next few years, so that the utilization of these drugs is included at an early stage.

For the second category of questions, participants also raised the need for more evidence on the effectiveness of PCSK9s including assessments of mortality benefit, use in primary prevention, and reductions in major CVD and ASCVD endpoints. This research could complement recently published clinical trials, like the FOURIER trial,² and could improve our understanding about how Sentinel’s data infrastructure could be leveraged to improve clinical trial efficiency.

Participants noted key challenges in using the Sentinel data infrastructure for generating PCSK9 evidence. For example, while Sentinel includes total cholesterol, HDL, and LDL in the common data model, additional resources would still be needed to curate the source data so they conform to this data model. This would be necessary to analyze the impact of PCSK9s on outcomes. In tandem with the curation step, participants observed that additional resources would also allow the data partners to establish new data streams that would increase the percentage of patients with lipid lab values. Also, it was noted that long-term (e.g. five or more years) tracking is difficult given the propensity for patients to switch health insurance plans, and therefore, other data sources, particularly electronic medical records, could be helpful this regard.

¹ Sentinel website: https://www.sentinelinitiative.org/background
Generating More Complete PCSK9 Evidence with Limited Extensions to the Data Infrastructure

Data linkages between Sentinel and other data networks could enable progress towards developing a more complete spectrum of PCSK9 evidence, from clinical effectiveness to understanding how these treatments can offer value to patients. These linkages, such as data from electronic health records or clinical registries, could provide additional lab results, diagnostic and pathology results, and clinical notes, which could allow for analyses on why a patient discontinues or switches therapies, the clinical reasons why indicated populations are not taking the therapy, or the indications for statin intolerance. This type of research could help inform important questions on how these treatments are used in real world practice settings, and the potential impact on coverage policies and value-based payment arrangements.

The workshop discussion highlighted potential opportunities for new data sources for the Sentinel Common Data Model. For example, it is expected the Sentinel System will soon include Centers for Medicare & Medicaid Services data in the near future, which will increase the amount of patient information stored in the system. Other potential data sources discussed were adding trusted sources of mortality data from the National Death Index, although there are noted time lags in this data, as well as registry data, such as that currently collected by the American College of Cardiology. Observational real-world treatment work done by the idiopathic pulmonary fibrosis community was given as an example of how patient data could also be leveraged into the Sentinel System model.

The National Patient-Centered Clinical Research Network, an innovative initiative of the Patient-Centered Outcomes Research Institute (PCORI), was highlighted as a possible opportunity to supplement Sentinel data with clinical data captured in electronic health records. Work is already underway to establish such a linkage between PCORnet and the Sentinel System with key findings to date presented at the workshop. While there are shared data elements between these common data models, the quality of data could differ and in some cases, only certain data elements are available in one data source. Table 1 overviews both unique and shared data elements between the PCORnet and Sentinel System's CDM.

In developing data linkages, a key challenge identified that would need to be addressed concerns the regulatory requirement of informed consent. These activities would likely be categorized as research and therefore patients would need to consent to having their data used. This becomes further complicated when data is used for cross network studies. For example, participants who have consented to participate in PCORnet studies would need to also consent to participation in studies featuring data linkages with the Sentinel System. Such a model would represent an open model of consent where patients either opt in or opt out of certain kinds of research. Developing such a model would require clear communication with patients on how their data could be used and for what purposes.

Participants thought the process for obtaining consent would also be an important consideration in facilitating the consent process. Consent is currently obtained through a variety of channels including paper-based or electronic (e.g. patient portals connected to electronic health records) and at different points in care delivery. Obtaining consent at the point of care could help facilitate research, and especially research embedded where patients routinely seek care. Participants noted an example of how Swedish catheterization laboratories are organized to obtain consent and facilitate immediate randomization of patients into study arms, which in part is made possible because of an established registry structure.
Table 1. Example Data Domains in Sentinel and PCORnet Common Data Models (with presenter’s permission)

<table>
<thead>
<tr>
<th>Sentinel Data Domains</th>
<th>PCORnet Data Domains</th>
<th>Areas of Domain Overlap</th>
</tr>
</thead>
<tbody>
<tr>
<td>Membership</td>
<td>Biospecimen &amp; Genomic Data</td>
<td>Conditions and Diagnoses</td>
</tr>
<tr>
<td>Claims</td>
<td>Patient Reported Outcomes</td>
<td>Vital Status</td>
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<tr>
<td>Drug Dispensing</td>
<td>Drug Prescribing</td>
<td>Demographics</td>
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<td></td>
<td>Lab Results</td>
<td>Procedures</td>
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<td></td>
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<td>Encounters</td>
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**Best Practices for Leveraging Sentinel’s Distributed Data Infrastructure**

Fully leveraging the mature capabilities, expertise, and resources available through Sentinel and its data infrastructure will also require a more refined understanding of the operational and administrative needs to coordinate research activities. Early experience is emerging from the implementation of Sentinel extension projects including the Reagan Udall Foundation’s Medical Evidence Development and Surveillance (IMEDS) program and the FDA-Catalyst initiative.

The IMEDS program provides access to Sentinel System’s data infrastructure, recently completed a pilot sponsored by Pfizer, which used an observational study design to test specific safety questions using the IMEDS distributed database and rapid query templates known as modular programs. The IMPACT-AFib trial is the first ever implementation of a randomized control trial (RCT) within the Sentinel infrastructure, which seeks to evaluate the use of direct mail to health plan members with atrial fibrillation and their providers to encourage consideration of oral anticoagulation for the prevention of stroke.

Although these studies used very different study designs, they each provided important lessons for future Sentinel extension projects. Both studies were executed as research and therefore required Institutional Review Board (IRB) approval. A common yet complex challenge faced by both studies related to the regulatory requirement of informed consent. The IMPACT-AFib trial and the IMEDS pilot both sought waivers of informed consent given the low risk nature of these studies, however, each experienced challenges coordinating this process. This is because some organizations had different legal requirements for participating in the study, which fragmented the approach for obtaining IRB approval.

In all, both studies demonstrated the feasibility, utility, and power of extending the Sentinel infrastructure. However, best practices and lessons learned are still needed to efficiently scale the design and implementation of research activities especially as they relate to the compliance with human subjects protections regulations.

**Conclusion**

The FDA’s Sentinel System, an active post-market safety surveillance system that allows for rapid and secure evaluation of medical product safety issues, is increasingly being recognized as a mature and robust data infrastructure that could be expanded for evidence generation beyond safety surveillance. This established infrastructure and partnership could serve as a resource to answer critical stakeholder questions on what medical products work best and for whom.

PCSK9 inhibitors, the new class of cholesterol-lowering medications, provide a good test case to explore the feasibility of leveraging Sentinel’s data infrastructure in this way. There remain unanswered questions on how these treatments are being used in real world populations, including the
characteristics of treated patient populations and prescribing trends among other key variables. Workshop participants commented on Sentinel’s unique capabilities to answer these questions through descriptive analyses in the short-term. In the longer-term the potential for more advanced analyses, such as assessing the impact of PCSK9 inhibitors on health outcomes, would require new methods and data modifications to incorporate data currently external to Sentinel’s common data model.

One key strategy raised throughout the workshop was to start with basic analyses and move towards more sophisticated analyses through an incremental and stepwise approach. Some participants thought current Sentinel capabilities could answer a range of questions about trends and short-term outcomes on PCSK9 inhibitors in real world practice settings. With this established baseline, future projects might consider incorporating new sources of data outside of Sentinel’s existing common data model to build a more complete dataset, including LDL-C data elements, for conducting more sophisticated analyses requiring randomization or pseudo-randomization to assess key clinical outcomes such as mortality benefit and major CVD and ACVD endpoints. To reach this longer term vision, an initial and step-wise approach might include demonstrating how Sentinel data infrastructure could be leveraged to support efficient trial conduct such as improving the speed of identifying eligible patients, randomizing them, and facilitating other key data capture processes.

This pragmatic approach will support the extension of Sentinel’s data infrastructure beyond safety surveillance, thus leveraging its unique ability to aggregate nationally representative data sets across partnering organizations to efficiently produce more generalizable evidence than what an individual organization could achieve on its own.