



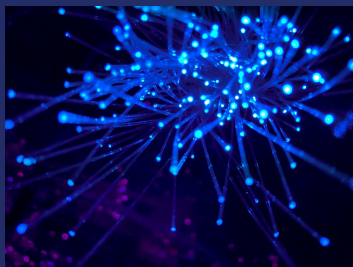
## Sentinel Newsletter

Fourth Quarter 2022

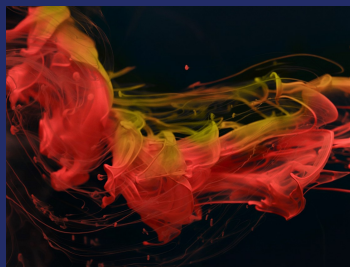
Explore the [Sentinel YouTube Channel](#) and [Sentinel Website](#) for more information.



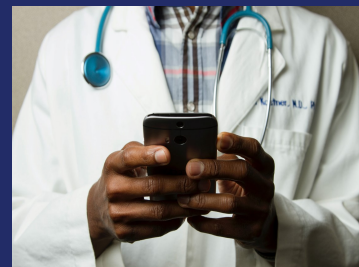
### In This Issue:



14th Annual Sentinel Public Workshop



Novel Methods for Pregnancy Drug Safety Surveillance in the FDA Sentinel System



Engage With Sentinel: An Overview of Webinars and Trainings from 2022

## 14th Annual Sentinel Public Meeting

On November 15<sup>th</sup> and 16<sup>th</sup>, the Duke-Margolis Center for Health Policy hosted the [Fourteenth Annual Sentinel Initiative Public Workshop](#).

The keynote of the workshop was delivered by the Director of the FDA Center for Drug Evaluation Research (CDER), Dr. Patrizia Cavazzoni. She highlighted the FDA's commitment under the Prescription Drug User Fee Act (PDUFA VI) which required an [assessment report](#) on Sentinel's use for regulatory purposes. She expanded on the results, stating that the Sentinel System contributed to 43 regulatory actions between 2017 and 2021, some of which include implementing label changes and contributions to drug safety communications. Dr. Cavazzoni commented that the Sentinel System's real-world data provides an important perspective in post-market surveillance. These real-world data resources, pulled from multiple data streams, better position the FDA to fulfill its mission to protect and promote public health through assessing the safety of FDA regulated medical products. Dr. Cavazzoni ended with a call to look ahead to the future of data, in particular the use of electronic health record (EHR) data with linked administrative



Dr. Patrizia Cavazzoni

## Novel Methods for Pregnancy Drug Safety Surveillance in the FDA Sentinel System

It is a priority of the US Food and Drug Administration (FDA) to evaluate the safety of medications used during pregnancy. Pregnancy exposure registries are a primary source of information and use prospective data collection to gather comprehensive patient level data for women exposed to specific medications during pregnancy. However, the pregnancy registries are often only powered to detect an increase in the risk of major congenital malformations as a single composite outcome and face challenges with enrollment and retention of patients. Cohort studies using administrative claims data can complement data from

insurance claims. She acknowledged the significance of EHR data on FDA's response to the COVID-19 pandemic and that FDA hopes to continue to further EHR and claims linked resources to support regulatory work.

The Workshop also featured a fireside chat with FDA Sentinel Initiative Leadership, Dr. Gerald Dal Pan (Director, Office of Surveillance & Epidemiology, CDER) and Dr. Steven Anderson (Director, Office of Biostatistics and Epidemiology, Center for Biologics Evaluation and Research (CBER)). Dr. Dal Pan covered major milestones for the Sentinel System, including the assessment of safety concerns with the Active Risk Identification and Analysis (ARIA) tools, and the work performed with each of the Sentinel Coordinating Centers over the past few years. He described how the Sentinel System has been leveraged to address emerging health issues, such as the COVID-19 pandemic. The Sentinel System was quick to adjust the frequency of existing data streams to access more recent data from standing data partners, in addition to bringing on new data partners to provide inpatient and ambulatory EHR data. Dr. Dal Pan finished by providing current considerations on the development of Sentinel, emphasizing the Sentinel Innovation Center's work building an EHR system with claims-linked data and transitioning to draw on those capabilities. Additionally, he noted that natural language processing (NLP) will allow Sentinel to address a broader range of health outcomes and that Sentinel will leverage signal identification more often to complement other post-marketing safety approaches.

Dr. Steven Anderson explained that the work done with the COVID-19 pandemic is now being expanded to a portfolio of work to include other epidemics, such as the Monkeypox outbreak. He described some of the work performed to identify safety signals for mRNA vaccines and highlighted the ongoing COVID-19 vaccine project that will involve a dozen studies monitoring different vaccines. Dr. Anderson mentioned the work occurring within CBER's individual coordinating centers, briefly touching upon the innovation center's NLP work to identify adverse events associated with administered biologic products and to semi-automate adverse event reporting in the future. He ended by discussing CBER's future goals that involve utilizing and expanding systems to accommodate new product needs.

Dr. Patricia Bright, Associate Director for Sentinel and Program Lead, reflected on successes of PDUFA VI and commitments required by PDUFA VII that directly involve the optimization of the Sentinel Initiative. These commitments include maintenance of the Sentinel Initiative capabilities, continued integration into FDA drug safety activities, and enhancement of the analytic capabilities. Additional sessions included presentations from the Sentinel Operations Center, highlighting recent studies on COVID-19, assessments of treatments, and updates on signal detection capabilities. Representatives from the Sentinel System and CBER's Biologics Effectiveness and Safety (BEST) Initiative delved into innovations within data infrastructure and analytic methods, showcasing how real-world data sources have been used in recent studies. The Workshop ended with a discussion on how to expand partnerships and build Sentinel's Stakeholder community, which involved leadership from the Community Building and Outreach Center (CBOC) and representatives from Centers for Disease Control and Prevention (CDC), IBM Consulting, and eHealth Exchange.

Presentation materials and a live recording can be found [here](#).

registries and have the advantage of identifying large numbers of pregnant women exposed to particular medications, but typically assess a limited number of outcomes.

Administrative data can be better leveraged by using TreeScan™, a statistical program and method, to assess multiple adverse infant outcomes simultaneously. A case study was completed using TreeScan and the FDA Sentinel analytic tools to assess the use of this method, in claims data, to identify infant outcomes after maternal medication use in pregnancy. First trimester fluoroquinolone use, and cephalosporin use were compared. Outcomes included major congenital malformations and gestational length and birth weight. The Bernoulli and Poisson TreeScan statistics were used with compatible propensity score-based study designs for confounding control (matching and stratification) and multiple propensity score models, to inform best practices for future analyses. A hierarchical outcome tree, including major congenital malformations and outcomes of gestational length and birth weight, was developed.

A total of 1,791 fluoroquinolone-exposed and 8,739 cephalosporin-exposed mother-infant pairs were eligible for analysis. The TreeScan analysis resulted in alerts for infant outcomes, which were deemed to be explained by differences between fluoroquinolone and cephalosporin users and otherwise not warranting follow-up. As expected, there were no new observed safety signals for fluoroquinolone use in the first trimester. TreeScan is a valuable tool, in addition to current safety surveillance methods, for medications used during pregnancy.

## [The 2022 Sentinel Innovation and Methods Seminar Series](#)

The Sentinel Innovation and Methods Seminar Series features presentations by leading experts and innovators on topics related to the work of the Innovation Center (IC) and the Sentinel Operations Center (SOC). The Seminar Series describes emerging approaches in real world data utilization such as feature extraction, natural language processing, machine learning, and techniques to advance causal inference improving Sentinel's capabilities.

Visit the [Sentinel Meetings, Workshops, & Trainings page](#) to view past seminars, webinars, and workshops and to register for upcoming events in 2022.

### **Past Seminars from 2022:**

- [January 28, 2022: An Introduction to Negative Control and Proximal Causal Learning](#)
- [February 24, 2022: Do All Roads Lead to FHIR? Imagining FHIR as a Meta-Common Data Model for Research](#)
- [March 28, 2022: Data Leakage Due to Care Provided Outside of the Study Electronic Health Record System: Potential Biases and Solutions](#)
- [May 11, 2022: Can We Train Machine Learning Methods to Outperform the High-Dimensional Propensity Score Algorithm?](#)
- [August 11, 2022: Advancing the Use of Real-World Evidence for Health Technology Assessment – The NICE Real-World Evidence Framework](#)
- [August 30, 2022: Representing and Utilizing Clinical Textual Data for Real World Studies: An OHDSI Approach](#)
- [September 7, 2022: Deep Learning on Electronic Health Records for Research in Pharmacoepidemiology: Examples From the Field of Oncology](#)
- [September 12, 2022: Machine Learning for High-dimensional Proxy Covariate Adjustment in Healthcare Database Studies: An Overview of the Current Literature](#)
- [September 26, 2022: Addressing Missing Data in Comparative Effectiveness Research Using EHR Data](#)

### **Upcoming Seminars in 2022:**

- [December 16: Machine Learning in Distributed Data Networks like the FDA Sentinel System: Opportunities, Challenges, and Considerations](#)

## **2022 Sentinel Community Building and Outreach Center (CBOC) Training Series**

### **CBOC Webinar Series**

The Community Building and Outreach Center has developed a webinar series to increase stakeholder awareness and engagement with the Sentinel System.

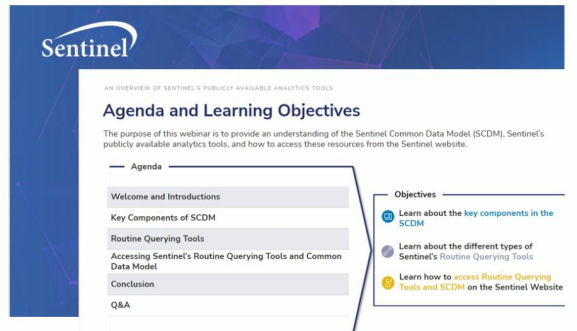
### **AN OVERVIEW OF THE SENTINEL WEBSITE FOR HEALTH ADVOCATES**

On January 19, 2022, CBOC hosted a webinar on how Health Advocates can use publicly available resources on the Sentinel website. The webinar provided an overview of the Sentinel System, explained how the Sentinel System protects health data, and how to navigate the [Sentinel website](#). The webinar reviewed how to find recent publications, presentations, reports of drug safety assessments, trainings, and workshop materials. [Please click the image below to access the webinar recording.](#)



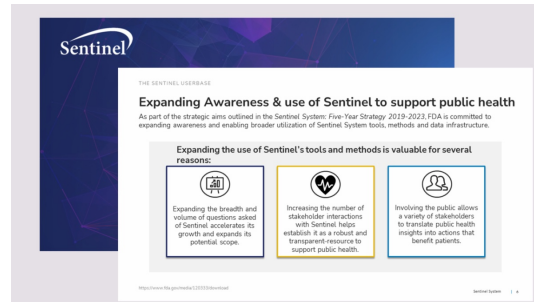
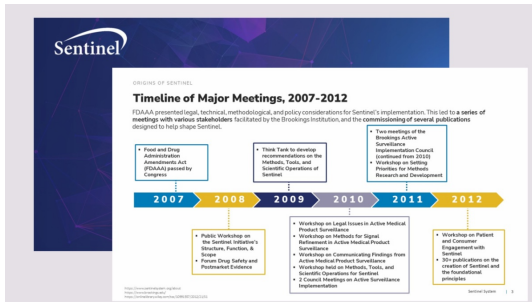
## AN OVERVIEW OF SENTINEL'S PUBLICLY AVAILABLE ANALYTIC TOOLS

On September 14, 2022, CBOC hosted a webinar to provide an understanding of Sentinel's publicly available analytic tools, the Sentinel Common Data Model, and how to access those resources from the Sentinel website. [Click on the image below to view a recording of the recently released webinar.](#)



## CBOC Informational Videos

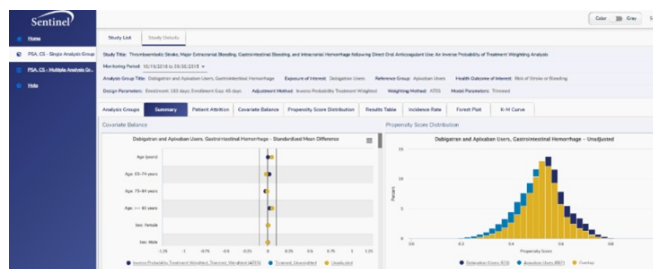
The Community Building and Outreach Center has created informational videos to provide on-demand resources to become more familiar with Sentinel. Click below to learn more about two recently released videos.



**MAJOR MOMENTS** details the key milestones in the evolution of Sentinel as a national resource, starting from the Mini-Sentinel pilot in 2009 to Sentinel today.

**THE SENTINEL USERBASE** highlights various groups of stakeholders that can use Sentinel as a resource to inform their work.

## CBOC Virtual Training Sessions



**SENTINEL VIEWS** is a data visualization application designed to increase access to the Sentinel System study results. It has been integrated into the existing Sentinel querying and reporting infrastructure, to support the Sentinel System's vision of serving as a [national resource](#) for medical product safety surveillance and real-world evidence generation.

## New Analytic Packages, Methods, Tools and Reports

### Methods and Tools Projects:

- [COVID-19 Pregnancy Study: Aim 3](#)
- [The Centers for Medicare and Medicaid Services \(CMS\): Medicaid and Children's Health Insurance Program \(CHIP\) Claims in Sentinel Common Data Model \(SCDM\) Format](#)
- [Sentinel Routine Querying System \(version 12.0.0\)](#)
- [Sentinel Routine Querying System Reporting Tool \(version 2.0.0\)](#)
- [Sentinel Data Quality Review and Characterization Programs](#)

### Reports:

- [Utilization of Ixekizumab in Pregnant Patients: A Descriptive Analysis](#)
- [Taltz \(Ixekizumab\) & Use in Pregnancy](#)
- [Ozempic \(semaglutide\) & Signal Identification](#)
- [Zarxio \(filgrastim-sndz\) & Signal Identification](#)
- [Outcome Monitoring Following Zarxio Use: A Signal Identification Analysis](#)
- [Outcome Monitoring Following Ozempic Use in Patients with Type 2 Diabetes: A Signal Identification Analysis](#)
- [Utilization of Ibrexafungerp in Pregnant Patients: A Descriptive Analysis](#)
- [Fractures Following Leuprolide Acetate Use: A Multiple Factor Matched Analysis \(A Follow-up to a Previous Analysis\)](#)

## Recent Publications and Presentations

- [Scalable Phenotyping for Safety Outcomes Using Electronic Health Record Data](#)
- [Assessing Medical Product Safety During Pregnancy using Parametrizable Tools in the Sentinel Distributed Database](#)
- [Improving Methods of Identifying Anaphylaxis for Medical Product Safety Surveillance Using Natural Language Processing and Machine Learning](#)
- [A New Analytic Tool for Assessing the Impact of the US Food and Drug Administration Regulatory Actions](#)
- [Association of COVID-19 vs Influenza with Risk of Arterial and Venous Thrombotic Events Among Hospitalized Patients](#)
- [Spironolactone Utilization among Patients with Reduced and Preserved Ejection Fraction Heart Failure](#)
- [Monitoring Drug Safety in Pregnancy with Scan Statistics: A Comparison of Two Study Designs](#)
- [COVID-19 Real-World Evidence Primer](#)
- [How Big Data Support Post Marketing Surveillance in USA: The Sentinel Initiative](#)
- [Should Insulin Billing Procedure Codes be Considered for Exposure Ascertainment in Pharmacoepidemiology Studies?](#)
- [Describing Prenatal Exposures and Evaluating Maternal and Infant Outcomes in Sentinel](#)

Explore the [Sentinel YouTube Channel](#) and [Sentinel Website](#) for more information.

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