MINI-SENTINEL CBER/PRISM SURVEILLANCE PROTOCOL

ACCESSING THE FRESHEST FEASIBLE DATA FOR CONDUCTING ACTIVE INFLUENZA VACCINE SAFETY SURVEILLANCE

Version 3.0

Prepared by: W. Katherine Yih, PhD, MPH,[1] Sukhminder Sandhu, PhD, MPH, MS [2], Michael Nguyen, MD,[2] Lauren Zichittella, MS,[1] Cheryl N McMahill-Walraven, PhD, MSW[3], Mano S. Selvan, PhD[4], Nandini Selvam, PhD, MPH[5], Ruihua Yin, MS,[1] Grace M. Lee, MD, MPH[1]

Author Affiliations: 1. Department of Population Medicine, Harvard Pilgrim Health Care Institute and Harvard Medical School, Boston, MA; 2. Center for Biologics Evaluation and Research, Food and Drug Administration, Rockville, MD; 3. Aetna Informatics, Aetna, Blue Bell, PA; 4. Comprehensive Health Insights, Humana Inc., Louisville, KY; 5. Government & Academic Research, HealthCore, Alexandria, VA

December 31, 2013

Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance. Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise. The Mini-Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223200910006I.

History of Modifications

Version	Date	Modification	By
V#2	08/30/2013	• Modified Section II, p. 2 to make it clear outcome of interest is *febrile* seizures, but justified using just "seizures" in most of document • Included, in Section V, pp. 4-5, intradermal as one of the specific vaccines for which monitoring of dose and case counts will be done • Updated Section V, p. 5 to say that dose and case counts will be monitored separately for the two quadrivalent inactivated vaccines • In Table 3, p. 10, last row, third to last column, removed superscript c from "LAIV"—unlike for IIV, where an increased risk of seizures was observed in the 2010-11 and 2011-12 seasons, there is no need to restrict post-LAIV seizure background rates to certain historical influenza seasons • Included, in Table 3, p. 10, last row, last column, a difference-in-difference analysis as a possible analysis to be done in the event of a signal in a current LAIV vs. historical IIV comparison • Included, in Table 3, p. 10, second row, last column, "2) current LAIV vs. current IIV regression and/or difference-in-difference analysis;" this was for the sake of consistency with the last row, last column; said in footnote that decision between the two analyses (regression vs. DiD) will be made in consultation with FDA • Included in Section X, pp. 13-14, sentences about what will happen in the case of a signal in a current LAIV vs. historical IIV comparison, to match the revised Table 3 • Included in Section XI, p. 14, the word "febrile," because here we are discussing chart review and do intend to use only febrile seizure cases in analyses of chart-confirmed cases	Mini-Sentinel PRISM Sequential Analysis Workgroup
V#3	12/10/2013	• Added to Section VIII.C., p. 12, the requirement that at least 4 events in risk and control intervals combined are necessary for a signal in the SCRI (binomial maxSPRT) analyses	Mini-Sentinel PRISM Sequential Analysis Workgroup

Mini-Sentinel CBER/PRISM Surveillance Protocol

Accessing the Freshest Feasible Data for Conducting Active Influenza Vaccine Safety Surveillance

Table of Contents

I. AIMS

The scope of work for this public health activity is to develop, implement, and evaluate sequential analysis for influenza vaccine safety surveillance with the Mini-Sentinel population. This includes selecting the health outcomes of interest, identifying and linking data sources relevant for the exposures and outcomes of interest, evaluating the availability and feasibility of using very recent data, checking data quality of source files and of aggregate files, conducting sequential analyses while adjusting for data lags or for partial data, and evaluating the fresh data compared to the mature data. There are four aims in this project:

1. To identify and evaluate sources of freshest possible data available from PRISM Data Partners
2. To establish a "sequential analysis system" that can use the freshest feasible data from PRISM Data Partners for sequential analysis activities
3. To evaluate the fresh data as compared to the mature data for the same period in the Mini-Sentinel Common Data Model
4. To conduct near real-time surveillance for two health outcomes of interest (HOIs) following influenza vaccination

The final report for this project will focus on Aim 4, incorporating high-level findings from Aims 1-3 as helpful for the interpretation of the Aim 4 results.

II. INTRODUCTION

Mini-Sentinel is a postmarket risk identification system for all FDA regulated products that was created to meet the legislative mandate of the FDA Amendments Act of 2007 and was initiated in 2009 with the Harvard Pilgrim Health Care Institute as the coordinating center. There are a total of 18 Data Partners that participate in Mini-Sentinel, covering 130 million individuals. The Post-licensure Rapid Immunization Safety Monitoring (PRISM) program was established within Mini-Sentinel to provide a national system for conducting active vaccine safety surveillance across four Data Partners covering up to 110 million individuals.

Influenza vaccine safety surveillance is challenging because the vaccines are given within a short span of time and may be administered outside of the traditional health care settings (e.g., schools, work). Currently, Mini-Sentinel data are refreshed on a quarterly basis and contain relatively settled and complete data, the most recent of which are on average 6-9 months old. Near real-time surveillance of influenza vaccines requires more frequent data updates and fresher data in each updated dataset if safety problems are to be detected in time to intervene. Influenza vaccines are routinely available in early September, and the majority of vaccines are distributed and administered by late November. This project aims to develop a new data pipeline to access fresher data on a more frequent basis in three of the four PRISM Data Partners. We plan to evaluate the usefulness of conducting surveillance with fresher data that is more timely but incomplete and requires more effort to utilize. Bi-monthly data

refreshes are planned, which, if staggered, will allow monthly analyses. Using fresher data will also require new methods to be employed to adjust for data lag and incomplete data.

Based on information from Aim 1, we plan to **pilot the sequential surveillance system** in Aims 2 and 3. The pilot has two objectives: a) to practice data extraction during the 2012-13 season, conduct data quality checks, and to work out any problems ahead of the 2013-14 season; and b) to allow, within the time-frame of the activity, evaluation of the fresh data as compared to the mature data for the same period in the Mini-Sentinel Common Data Model. The latter objective will be performed in 2014 after data become available for comparison from the Common Data Model. We will also **implement prospective surveillance** during the 2013-14 season. We plan to monitor a very rare condition and a more common condition—anaphylaxis and febrile seizures, respectively—which require different study designs for surveillance. (In what follows, we will generally refer to the second as simply "seizures," as in surveillance using administrative data we will not distinguish between febrile and afebrile seizures. The distinction will be made and febrile seizures used for analysis only if a signal arises and chart review is done.) This project is considered active public health surveillance and hypothesis generating.

III. STUDY PERIOD AND POPULATION

For Aim 1, we conducted surveys and queries with our Data Partners via e-mail and conference calls in the first half of 2012. For Aims 2 and 3, we include health plan data from the Mini-Sentinel PRISM cohort on vaccine exposure and outcomes for encounters occurring during the 2012-13 influenza season. Three of PRISM's four Data Partners are participating: Aetna, HealthCore, and Humana. Data Partners were asked to conduct three data refreshes during the 2012-13 influenza season. These sequential data files will be compared to data from the Common Data Model when it becomes available, in early 2014.

For Aim 4, prospective surveillance during the 2013-14 influenza season, we include both health plan data on vaccine exposure and outcomes and state immunization registry data on vaccine exposure. The participating immunization registries are in FL, IN, PA, MI, MN, NY City, NY State, VA, and WI. For purposes of matching members to immunization registries, we will use a list of members enrolled at each health plan as of October 1, 2013.

During the 2013-14 surveillance season, we will have resources available to conduct three data refreshes for each Data Partner (DP) and one immunization registry match. As feasible, we will stagger the data refreshes, along the lines shown below, for example:

- October – DP 1
- November - DP 2 and 3
- December - DP 1
- January – DP 2 and 3
- February – DP 1
- March – DP 2 and 3

By staggering the data refreshes, we can conduct monthly refreshes and analyses throughout the season, while minimizing the burden to Data Partners.

Table 1 summarizes the purposes, population, and immunization registry use of the two influenza seasons to be studied in this project.

Table 1. Purposes, population, and immunization registry use in two influenza seasons to be studied

Influenza season to be studied	Purposes	Population included in surveillance	Immunization registry match	Time of membership pull for match
2012-13	1) Practice for 2013-14; 2) comparison of freshest feasible data with mature (MSCDM) data	Those vaccinated for influenza on or after 9/1/2012 (up to 4/30/2013 maximum) among those with any medical claim on or after 9/1/2012	None	N.a.
2013-14	Safety surveillance	Those vaccinated for influenza on or after 9/1/2013 (up to 4/30/2014 maximum*) among those with any medical claim on or after 9/1/2012	One, in Jan. 2014	Oct. 2013

* Actual last vaccination date expected is 2/28/2014, given planned schedule of data extractions.

IV. DATA SOURCES AND TERMINOLOGY

For Aim 1, we conducted surveys and queries with the Data Partners via e-mail and conference calls in the first half of 2012. We have identified the freshest *possible* data that could be used to monitor vaccine safety in an emergency situation such as a pandemic, as well as the freshest *feasible* data, which will be used for Aims 2-4. The costs of freshest *possible* data are considerably higher than of freshest *feasible* data.

We call the freshest feasible data sources we are targeting for Aims 2-4 "sequential source files" (SSFs). The Data Partners have their own specific terms for these. We have written specifications for the Data Partners to use in converting these SSFs into uniform-format member-level files, which we call "sequential data files" (SDFs). Below is some terminology for the data or file types discussed in this protocol:

1. Mini-Sentinel Common data model (MSCDM): Prepared by Data Partners for use in other Mini-Sentinel activities. Person-level, not member-level. ("Members" are distinguished by policy numbers; one unique person can correspond to more than one "member" due, for example, to disenrollment and reenrollment.) Updated on quarterly schedule. Most recent data generally excluded, favoring reliability over timeliness.
2. Freshest possible data (FPD): The earliest files available to the Data Partner may contain unprocessed claims as they arrive into the Data Partner's data warehouse. FPD would be the most timely data source. Due to resource constraints, we will not pursue these files at this time (except for the Data Partner mentioned in Item 3 immediately below).

3. Sequential Source Files (SSFs): The internal files at each Data Partner we are actually targeting for Aims 2-4. These files include only claims that are adjudicated or—if no reimbursement is expected—recorded (e.g., for capitated health plans where providers are reimbursed for monthly management of the member's health care, not reimbursed for every service provided; or for vaccines obtained using a state-purchasing program and not submitted for reimbursement after administration; etc.) For one Data Partner, the SSFs are the same as the FPD.
4. Sequential Data Files (SDFs): Developed by programmers at each Data Partner by translating SSFs to a common data model, using specifications provided by the PRISM coordinating center, for Aims 2-4. Compared with the Mini-Sentinel CDM, the goal of the SDFs is to provide more timely and streamlined data, targeting a population with medical claims on or after September 1, 2012 (regardless of influenza vaccination status) and selecting claims data on vaccine exposures and health care encounters, linked to demographic information. Of note, we will not require enrollment data with these monthly refreshes. Rather, enrollment data will be used only to identify members as of October 1, 2013 in order to conduct the match with immunization registries.
5. Sequential Case Files (SCFs): Subset of the SDFs created to preserve demographic, medical claim, and dispensing data for cases of interest. All generations of SCFs will be saved by the Data Partners to facilitate the creation of aggregated datasets for analysis, the assessment of data flux over time, and for chart review if a signal is detected.
6. Sequential Aggregate (or Analysis) Files (SAFs): Analysis files produced when Data Partners run an aggregation program written by PRISM coordinating center programmers on the SDFs and SCFs. SAFs are no longer member-level data but rather will contain a summary count of the number of members in each stratum defined by certain characteristics. SAFs will consist of a vaccine summary file ("VSUM") and a diagnosis summary file ("DXSUM"). Variables defining the strata will include week of vaccination, age group, sex, vaccine type, certain concomitant vaccines, dose number, and, in DXSUM, HOI and timing of HOI relative to the vaccine of interest.

V. VACCINE EXPOSURES

Influenza vaccination will be ascertained by a variety of code types, including CPT, CVX, HCPCS, and NDC codes. Distinction among specific vaccine products will be imperfect except where NDCs are used, manufacturer information is available in registry data, or a CPT, CVX, or HCPCS code corresponds to a single product type.

We plan to do separate sequential analyses for live attenuated influenza vaccine and (pooled) inactivated influenza vaccines. If there are "not otherwise specified" influenza vaccines in our data, we will combine them with pooled inactivated influenza vaccines, considering that those are more commonly used than the live attenuated vaccines. We recognize the desirability of analyzing specific vaccine products separately, especially in view of the newer, qualitatively different products such as the intradermal, cell-based, high-dose, quadrivalent, and recombinant vaccines. However, the counts of HOIs after each of these specific vaccines are expected to be too low to produce useful results in separate statistical analysis. Therefore, all inactivated influenza vaccines will be combined for sequential

analysis, but we will also show dose and HOIs counts for the intradermal, cell-based, high-dose, recombinant, and two quadrivalent inactivated vaccines separately,, without statistical analysis.

Claims of influenza vaccine received by a member within 14 days of a prior dose will be considered duplicates

Because of the increased risk of febrile seizures observed after concomitant vaccination with Dose 1 inactivated influenza vaccine and PCV13 in young children,[1] analyses of seizures in the 6-23 month old age group will be stratified by whether or not there was concomitant PCV13 vaccination. Like influenza vaccination, PCV13 vaccination will be ascertained by means of a variety of code types.

VI. HEALTH OUTCOMES OF INTEREST

The two health outcomes we will monitor are anaphylaxis and seizures. For each of these, to increase the positive predictive value (at the expense of sensitivity) and to reduce our capture of follow-up encounters, we will count cases only from inpatient and emergency department (ED) settings, and we will count only first encounters with an ICD-9 code of interest within a 6-month period of time. We will monitor seizures only in children less than 5 years of age. We divide seizures into three separate "outcomes" by age group and concomitant PCV13 status. The definitions of these outcomes, with their risk and control intervals, are presented in Table 2. For convenience, we use the abbreviations "IIV" and "LAIV" to refer to inactivated influenza vaccines and live attenuated vaccine, respectively.

Table 2. HOI definitions; "IIV" and "LAIV" to refer to inactivated influenza vaccines and live attenuated vaccine, respectively

HOI	Codes	Flu vaccine type	Age group	Setting	Risk interval	Control interval	First in what period?[a]	Other exclusions
1. Anaphylaxis	995.0 999.4	All	IIV: ≥6m LAIV: 2-49 y	Inpat or ED	0-1 days	0-1 days after IIV in historical data, even for LAIV analyses[b]	6 mo., inpat or ED setting	None
2. Seizures in youngest, concomitant PCV13	780.3 (Convulsions) 780.31 (Febrile) 780.32 (Complex) 780.39 (Other)	IIV[c]	6-23 m	Inpat or ED	0-1 days[d]	14-20 days[e]	6 mo., any setting (incl outpt)	None
3. Seizures in youngest, no concomitant PCV13	Ditto	IIV[c]	6-23 m	Inpat or ED	0-1 days[d]	14-20 days[e]	6 mo., any setting (incl outpt)	None
4. Seizures	Ditto	All[f]	24-59 m	Inpat or ED	For IIV: 0-1 days[d] For LAIV: 1-3 days[d]	For IIV: 14-20 days[e] For LAIV: 15-20 days[e]	6 mo., any setting (incl outpt)	None

[a] Not all cases will have a full look-back period of prior data, so the look-back period will be either 6 months or, if that full period is not available, the maximum period available. Also, the fresh data sources to be used distinguish among member IDs, not unique individuals. Therefore, the look-back for previous diagnoses of anaphylaxis or seizures will be within member ID, not person ID. For example, if a person had a seizure and then switched health plans/products (leading to a change in member ID) before having a post-vaccination seizure, the earlier one would be overlooked in the electronic look-back.

[b] Historical data on anaphylaxis after LAIV are typically very sparse, so post-IIV historical rates will be used instead of post-LAIV historical rates.

[c] Fluzone & Fluzone Quadrivalent are the only influenza vaccines approved for use in this age group, thus most of the IIV identified in this group will be those vaccines.

[d] Seizures risk windows after IIV and LAIV are based on Rowhani-Rahbar et al.[2]

[e] The seizures control intervals shown are for the primary, self-controlled risk interval design. For the secondary, current vs. historical design, see Table 3.

[f] Not all vaccines are approved for use in this age group; most of the IIV identified in this group will be the approved vaccines.

VII. COMPARISON OF FRESH DATA VS. MATURE DATA

We will evaluate the system against the MSCDM, using data from the *2012-13* season. The Data Partners created SDFs, SCFs, and SAFs three times during the 2012-13 season. Each data refresh included cumulative data from September 2012 through the last available month in the SSFs. The three generations of SAFs are stored at the PRISM coordinating center.

In order to compare fresh vs. mature data, we will conduct analyses using the SAFs vs. CDM files. For the SAF data, we will apply data lag adjustments; analyze the aggregate data (without adjusting for multiple testing); and report observed and expected counts (and observed seizures counts in risk and comparison intervals) and the risk estimate for each of the outcomes. When the earliest generation of the MSCDM deemed to contain $\geq$ 90% complete data through March 2013 is available (assumed to be in early 2014), we will perform the same analyses using that data source. No data lag adjustment will be implemented for the MSCDM, although data will be truncated to create a dataset covering the same period as covered by the SAFs. In this way, we will be able to compare case counts and risk estimates from the fresh data sources at three points during the 2012-13 season as well as between the last batch of fresh data and the more mature MSCDM.

The main question we are seeking to answer with this portion of the evaluation, which concerns the 2012-13 season (Aim 3), is not whether there is an association between vaccine and HOI—and therefore there will be no signal evaluation/refinement for Aim 3—but rather whether the sequential analyses produced qualitatively similar results to analyses using the same design but the more complete and mature data available in the MSCDM. The MSCDM differs from the fresher data not only in its completeness but also in its distinction of unique persons rather than "members," of which there may be several per unique person. (Recall that "members" are distinguished by policy numbers; one unique person can correspond to more than one "member" due, for example, to disenrollment and reenrollment.)

In addition to this comparison of 2012-13 freshest feasible data to CDM data, we will assess the flux in the fresh data sources from one pull to the next in the 2013-14 season, using the multiple generations of SCFs.

VIII. SEQUENTIAL ANALYSIS DESIGNS AND STATISTICAL METHODS

A. THE DESIGNS

For prospective active surveillance in Aim 4, we propose to use the following approaches to evaluate whether or not an elevated risk exists:

- Self-controlled risk interval design, for seizures (primary)
- Current vs. historical comparison, for anaphylaxis (primary) and seizures (secondary)

Using the self-controlled risk interval (SCRI) design,[3-6] we will determine the cumulative number of **seizures** in the risk interval and compare it to the cumulative number in the control interval, adjusting

for unequal interval lengths. The SCRI design is our preferred approach for influenza vaccine safety monitoring since we can control for fixed potential confounders of interest, such as gender and co-morbidities. One of the limitations of using the SCRI design in near real time surveillance is that time-varying confounders, such as age and seasonality, may bias our findings. However, confounding due to seasonality is mitigated by the short duration of the risk and control windows, which both occur within a 21-day period. Another limitation is that for rare HOIs, we may not have sufficient power to detect signals in a timely fashion, particularly if the effect size is modest.

In the current vs. historical comparison, the cumulative number of **anaphylaxis** events in the risk interval following IIV or LAIV during the 2013-14 season will be compared with the number expected based on the rate in IIV vaccinees from historical seasons.[3] This approach is used in sequential analysis for rare outcomes such as anaphylaxis, because it has better power to detect a small RR and would detect a signal earlier given the same RR compared to most comparisons with concurrent controls, including the self-controlled risk interval approach. The limitation of the current-vs.-historical approach is that historical influenza vaccinees may not be an entirely appropriate comparison group for the influenza vaccinees in the season of interest. Confounding may exist due to different population characteristics or secular trends in anaphylaxis diagnoses over time (although we would attempt to identify and adjust for any secular trends before starting surveillance). If a signal occurs using this approach, we will need to recognize the possible biases introduced by this comparison.

Because of the limitation of greater-time-to-signal with the SCRI design, we will also use current vs. historical comparison as a secondary surveillance method for **seizures**. This will allow us to detect an increased risk earlier than the SCRI method. A subsequent signal detected using the SCRI method would reinforce the earlier signal. To monitor the safety of LAIV, we will conduct two current-vs.-historical comparisons, one using historical rates of seizures after LAIV, the other using historical rates after IIV, thereby addressing the questions of whether the quadrivalent LAIV used in 2013-14 is as safe as trivalent LAIVs historically and whether it is as safe as trivalent IIVs historically.

The various sequential analyses and comparisons are summarized in Table 3.

B. MAXIMIZED SEQUENTIAL PROBABILITY RATIO TEST (MAXSPRT)

With both designs, the Maximized Sequential Probability Ratio Test (maxSPRT) will be used to adjust for the repeated looks at the accumulating data.[7] There are two basic variants, one for Poisson data, which we will use for the current vs. historical comparison of anaphylaxis and of seizures, and the other for binomial data, which we will use for the SCRI analysis of seizures. The null hypothesis of no increased risk will be rejected if the test statistic, the log likelihood ratio (LLR), reaches an upper bound, the "critical value" of the LLR. The null hypothesis will not be rejected if the total number of cases of the HOI surpasses the pre-specified "upper limit" for surveillance, or if surveillance ends without reaching this upper limit (and if the LLR has not reached the critical value). The "total number of cases of the HOI" refers to the total number *expected* in the case of the Poisson maxSPRT and to the total number *observed* in the risk and control intervals in the case of the binomial maxSPRT.

Similar to the Poisson maxSPRT, the Conditional maxSPRT (CmaxSPRT) allows for a comparison of current counts to counts that would be expected based on historical rates, but it does not assume that historical rates are known without error.[8] In other words, the CmaxSPRT accounts for uncertainty in

historical rates. Guided by the results reported in the original CmaxSPRT method paper,[8] we will use the CmaxSPRT instead of the Poisson maxSPRT if the number of cases in the historical data used to obtain the background rates is less than 5 times the upper limit.

For each HOI, the critical value of the LLR is dictated by the user-specified upper limit of expected (for Poisson maxSPRT) or observed (for binomial maxSPRT and CmaxSPRT) events and alpha level. Upper limits will be selected based on the approximate number of events that would be expected under the null hypothesis in the risk interval (for Poisson maxSPRT) or in the risk plus control intervals (for binomial maxSPRT). For the current vs. historical comparison, the null hypothesis is that the risk after influenza vaccination in 2013-14 is no greater than the risk after influenza vaccination in past seasons. For the self-controlled risk interval comparison, the null hypothesis is that the risk after influenza vaccination in 2013-14 is no greater than the risk in a control period during the same season for those same individuals. The upper limit will be determined based on the incidence of anaphylaxis and seizures in the Mini-Sentinel population, as seen in several previous influenza seasons, together with the expected number of vaccines to be administered in the Mini-Sentinel population in 2013-14. If upper limits are reached before all cases in 2013-14 occur, the power will be lower than what would have been possible with a higher upper limit. Therefore, upper limits will be chosen such that they are slightly higher than the number of events actually expected to occur.

One-tailed tests will be used, looking only for elevated risks from vaccination rather than protective effects. Alpha will be 0.05.

If no signal emerges, the last sequential test or tests for each of the four outcomes will serve as the end-of-season analysis for that outcome (Table 3).

See the “Signal refinement” section below for the plans in the event of a signal.

Table 3. Sequential and end-of-season analyses

HOI	Flu vaccine type	Age group	1° sequential analysis method	2° sequential analysis method	Risk interval	Control interval for SCRI	Historical data to be used for current vs. historical comparison	End of season analysis <u>if no signal</u>	End of season analysis <u>if signal</u>, using chart-confirmed cases*
1. Anaphylaxis	IIV	≥6m	Current vs. historical	n.a.	0-1 days	n.a.	0-1 days post-IIV	Last sequential test	Non-sequential SCRI*
1. Anaphylaxis	LAIV	2-49 y	Current vs. historical	n.a.	0-1 days	n.a.	0-1 days post-**IIV**[a]	Last sequential test[a]	1) Non-sequential SCRI and 2) current LAIV vs. current IIV regression and/or difference-in-difference analysis*
2. Seizures in youngest, concomitant PCV13	IIV	6-23 m	SCRI	Current vs. historical	0-1 days[b]	14-20 days	0-1 days post-IIV[c]	Last sequential tests: SCRI (1°) and current vs. historical (2°)	None[d]
3. Seizures in youngest, **no** concomitant PCV13	IIV	6-23 m	SCRI	Current vs. historical	0-1 days[b]	14-20 days	0-1 days post-IIV[c]	Last sequential tests: SCRI (1°) and current vs. historical (2°)	None[d]
4. Seizures	IIV	24-59 m	SCRI	Current vs. historical	0-1 days[b]	14-20 days	0-1 days post-IIV[c]	Last sequential tests: SCRI (1°) and current vs. historical (2°)	None[d]
4. Seizures	LAIV	24-59 m	SCRI	Current vs. historical (**two**)	1-3 days[b]	15-20 days	1-3 days post-LAIV **and** 0-1 days post-IIV[c], with rate augmented by 50% to match 3-day post-LAIV risk interval	Last sequential tests: SCRI (1°) and current vs. historical (2°) (**two**)	1) Non-sequential SCRI; but if signal is in current LAIV vs. historical IIV comparison, then 2) current LAIV vs. current IIV regression and/or difference-in-difference analysis*

* Due to resource constraints, chart review will be conducted for at most 1 signal (i.e. row in the table). If > 1 signals emerge during sequential analysis, the choice of vaccine-outcome pair for chart review and study design will be made in consultation with FDA.

[a] Historical data on anaphylaxis after LAIV are typically very sparse, so post-IIV historical rates will be used instead of post-LAIV historical rates.

[b] Seizures risk windows after IIV and LAIV are based on Rowhani-Rahbar et al.[2]

[c] The historical rates to be used will be from prior to 7/2010, which is also largely prior to any concomitant PCV13 usage. The purpose of this restriction is to exclude influenza seasons in which the risk of post-IIV seizure was elevated and to exclude most concomitant PCV13.
[d] No end-of-season analysis using chart-confirmed cases is planned, because a signal would not be unexpected, and at least one other national vaccine safety surveillance system will be monitoring this outcome.

C. CONTINUOUS VS. GROUP SEQUENTIAL ANALYSIS

Because this is a proof-of-concept project for a situation in which relatively frequent updating of data would be expected, we will use *continuous* sequential analysis rather than adapt the methods for *group* sequential analysis. Under conditions of frequent data updates, continuous sequential methods will detect signals earlier for the same levels of alpha and power [Kulldorff, Silva 2012 presentations]. We will specify and build into the analyses the requirement that at least 3 events are necessary for a signal using the current vs. historical comparison (Poisson maxSPRT or CmaxSPRT); this is to avoid spurious signaling that would otherwise be possible due to a chance early occurrence of 1-2 rare events. For SCRI (binomial maxSPRT) analyses, we will build in the requirement that at least 4 events in risk and control intervals combined are necessary for a signal; this is to optimize power and the expected time to signal.

IX. DATA PROCESSES

A. SSFS, SDFS, AND AGGREGATE DATA FILE PROCESSING

The SSFs are refreshed at the Data Partner sites once a month, typically around mid-month. Each new version of the SSFs includes data through the end of the prior calendar month. On a bi-monthly basis, after the SSFs become available, the Data Partners will translate their SSFs to the standardized format provided by the PRISM coordinating center to create the SDFs. The coordinating center will write a QC program for the Data Partners to run on the SDFs each time. In addition to checking data attributes and adherence to the PRISM SDF model, the QC program will compare the SDFs with the previous set in order to ensure that cumulative counts of vaccinations increased, that the format of the contents (e.g. character vs. numeric, variable length) remained stable, etc. and will summarize other features of the current SDFs. Output will go to the coordinating center for evaluation.

After QC of the SDFs, the Data Partners will create the SCFs by running a program written by programmers at the PRISM coordinating center. The SCFs will be a subset of the SDFs and consist of members identified as cases of interest. This member-level data will be retained by Data Partners and used to analyze data flux and characteristics. It will also serve as the source data for the SAF diagnosis summary dataset and to complete chart identification in the event of a signal.

Following creation of the SCFs, a program written by PRISM coordinating center programmers will be run by Data Partners to create the SAFs. The SAFs will provide summarized vaccination and diagnosis data by stratum using cumulative data, dated from September 1, 2013 onward, found in the SDFs and SCFs. An example of a stratum in the vaccine file would be women 25-49 years old vaccinated with a first dose of LAIV during the week of October 20, 2013. The SAFs will be transferred to the coordinating center analysts via secure file transport for assessment and analysis.

B. BACKGROUND RATES

Background rates are needed to calculate expected counts of the HOIs and to specify upper limits for surveillance for the sequential analyses. These will be obtained from historical data in the MSCDM by means of Mini-Sentinel's Modular Program 3 and programs written by PRISM programmers, to be run by the Data Partners.

C. SEQUENTIAL ANALYSES AND ADJUSTMENTS FOR INCOMPLETE DATA

As mentioned above, the Poisson maxSPRT (or CmaxSPRT if appropriate) will be used for both anaphylaxis and seizures, and the binomial maxSPRT for the seizures outcomes. For both of these methods, we will conduct analyses using recent and therefore incompletely accrued data in order to obtain timely results. There are two kinds of adjustment usually needed for incomplete data. One is for observation intervals that have not yet fully elapsed. For the current vs. historical (Poisson maxSPRT) analysis, expected events are multiplied by the proportion of the risk interval that has elapsed. However, with the particular HOIs to be monitored in this project, this will not be needed, as the risk intervals are all less than 1 week long. For the self-controlled (binomial maxSPRT) analysis, we will wait for both risk and control intervals to elapse before including cases in the risk and control intervals associated with a particular vaccination week in analysis.

The other kind of adjustment needed is for lag in the arrival of HOI data. For this, we first obtain detailed quantitative information about data accrual by week after care date that is specific to Data Partner and medical setting. For the current vs. historical (Poisson maxSPRT) analysis, we multiply the expected by the fraction of HOI data expected to have arrived. For example, if for a particular stratum of our data (a) there were only 2 weeks between the vaccination week and the last possible care date in the batch of data, (b) there are 3.3 expected cases of the HOI based on background rates (and proportion of risk interval elapsed), (c) 75% of the cases of this HOI usually occur in the ED setting and 25% in the inpatient setting (known from prior analysis of historical data), and (d) in 2 weeks' time 60% of ED data accrue and 5% of inpatient data accrue (known from prior analysis of historical data), then the adjusted number of expected cases is 3.3 x ((75% x 60%) + (25% x 5%)) =1.5 expected events. For the self-controlled (binomial maxSPRT) analysis, we will not include events in the risk and control intervals associated with a vaccination week in the analysis until those intervals have elapsed (as mentioned above) *and* data for both risk and control intervals are determined to be $\geq$ 85% complete, according to the above-mentioned data accrual reports. These procedures have been documented and published by Greene et al.[9]

After each sequential analysis, a summary report will be generated showing the cumulative number of doses and, for each outcome, the cumulative number of cases in the risk interval, the number expected in the risk interval and (for seizures) observed in the control interval, the relative risk, the LLR, and an indicator of whether a signal has appeared, i.e. whether the LLR has surpassed the critical value.

D. FREQUENCY OF DATA REFRESHES AND OF SEQUENTIAL ANALYSES

We expect some variability in the timing of SSF and SDF creation at each refresh, both among and within Data Partners. But by following the schedule in the "Study period and population" section, we expect to be able to conduct sequential analyses with new (augmented) data in each on at least a monthly basis.

E. IMMUNIZATION REGISTRIES

Data on influenza and concomitant PCV 13 vaccination from state and New York City's immunization registries will be incorporated into sequential analysis just once during the 2013-14 season, in January

2014. Data Partners will provide lists of enrolled members as of October 1, 2013 to some or all of the nine participating immunization registries, according to the existence of data-sharing agreements between the parties. The registries will then return immunization data for these members to the Data Partners, who will convert the data into the MSCDM standard State Vaccine file format.

The PRISM coordinating center has written a QC program for Data Partners to run on their State Vaccine files. They will run this after building their State Vaccine file, returning the results to the coordinating center for evaluation. When data quality has been approved, the file will be referenced during the aggregation process, such that vaccination data from state registries are incorporated into VSUM and DXSUM.

F. FILE STORAGE

The following files will be saved per Mini-Sentinel procedures:

2012-13 season (see Evaluation of System section)
- SCFs, all 3 generations, at Data Partners
- SAFs, all 3 generations, at coordinating center

2013-14 season
- The most recent generation of complete SDFs and State Vaccine files, at Data Partners; last ones must be saved until the end of the project (Dec. 2014)
- SCFs, all generations, at Data Partners
- SAFs, all generations, at coordinating center

X. SIGNAL REFINEMENT

If a signal appears, we will first check the various inputs, including background rates, and follow other established procedures for investigating sequential analysis signals.[10] Ultimately, if the signal persists after these investigations, the response will depend on the HOI. In the event of a signal for any of the seizures outcomes in association with IIV, no chart-review or additional analysis will be conducted, because the magnitude of risk observed in the CDC-sponsored Vaccine Safety Datalink, with or without concomitant PCV13, in recent seasons was not considered great enough to alter vaccination recommendations. If a signal emerges and persists for anaphylaxis, chart review will be carried out and an end-of-season SCRI analysis done, using the chart-confirmed cases and a control interval of Days 7-8 after vaccination. If the signal is in the LAIV vs. historical IIV comparison, a current-season LAIV vs. current-season IIV regression analysis and/or a difference-in-difference analysis[4] will be done in addition. If a signal emerges and persists for seizures after LAIV, chart review will be conducted and an end-of-season SCRI analysis done. If the LAIV-seizures signal occurs in the LAIV vs. historical IIV comparison, we will do a regression analysis of current-season LAIV vs. current-season IIV and/or a difference-in-difference analysis.

Due to resource constraints, chart review will be conducted for at most 1 signal, i.e. at most 1 row in Table 3. If > 1 signals emerge during sequential analysis, the choice of outcome for further analysis with chart-confirmed cases will be made in consultation with FDA. Likewise, if there is a signal in the LAIV vs.

historical IIV comparison, the choice of end-of-season study design (regression vs. difference-in-difference) will be made in consultation with FDA.

These plans are summarized in the right-hand column of Table 3.

XI. VALIDATION OF HEALTH OUTCOMES VIA MEDICAL RECORD REVIEW

In the event of a signal during sequential analysis that cannot be ruled out in the course of implementing other established procedures for investigating sequential analysis signals,[10] charts will be sought for algorithm-identified cases and abstracted. The cases whose charts are obtained will be adjudicated and classified according to Brighton Collaboration criteria in the case of anaphylaxis and according to PRISM criteria in the case of febrile seizures. Both abstractors and adjudicators will be blinded to the timing of vaccination. In addition, records likely to contain influenza vaccination information will be sought and reviewed for the confirmed cases. We elaborate on the procedures for chart review and adjudication below:

In view of the fact that cases sometimes have medical services provided by multiple healthcare providers (e.g. an anaphylaxis case could have an ambulance ride, ER evaluation, treatment for cardiac arrest), PRISM clinical investigators will rank the HOI-related and the vaccination-related encounters of each case, based on which seem most likely to produce the most definitive diagnostic and vaccination information, respectively. The ranked lists will be returned to the Data Partners. The Data Partners will then attach member name, member birth date, member gender, provider name, and provider address to the visits. A PRISM program to be run at each Data Partner site will organize the list of providers of whom to request medical charts that include the medical encounter of interest (for vaccination or treatment for the HOI).

Each Data Partner will identify a preferred vendor to seek the charts. The charts will consist of specific items that need to be photocopied or scanned by the Data Partner's chart-review vendor. Examples of such items include the admission note, daily notes during hospitalization, discharge summary, neurology or other specialist reports, and diagnostic procedure results. Using a standardized extraction form, the chart-review vendor will notify the facilities, contact them to obtain the charts, photocopy or scan the appropriate pages of the chart, and redact the record of all personal identifiers. The Data Partners will have the option of reviewing the redacted records to ensure that the redaction is complete. The redacted charts will be uploaded to a secure portal at the Mini-Sentinel operations center for further review and abstraction by the PRISM team prior to medical chart adjudication.

Two adjudicators will independently review and classify 20 cases, blinded to vaccination history as well as to the other adjudicator's decision. Comparison of the two adjudicators' classifications will be used to refine the classification rules. Using the refined set of rules, adjudicators will complete a second round of case classification on an additional 20 cases. If there are zero discrepancies between adjudicators after the second round, then the remainder of the cases will distributed between the two adjudicators, with none except the initial 40 being reviewed by both. If there are any discrepancies between the adjudicators regarding the second batch of 20 cases, double-review of each subsequent case may be needed.

Symptom onset dates as determined by the adjudicators will be used to determine the interval between vaccination and HOI for the statistical analyses using chart-confirmed cases.

XII. REFERENCES

1. Tse A, Tseng HF, Greene SK, Vellozzi C, Lee GM. Signal identification and evaluation for risk of febrile seizures in children following trivalent inactivated influenza vaccine in the Vaccine Safety Datalink Project, 2010-2011. *Vaccine.* Mar 2 2012;30(11):2024-2031.
2. Rowhani-Rahbar A, Klein NP, Dekker CL, et al. Biologically plausible and evidence-based risk intervals in immunization safety research. *Vaccine.* Jul 24 2012.
3. Lee GM, Greene SK, Weintraub ES, et al. H1N1 and seasonal influenza vaccine safety in the vaccine safety datalink project. *American journal of preventive medicine.* Aug 2011;41(2):121-128.
4. Greene SK, Kulldorff M, Lewis EM, et al. Near real-time surveillance for influenza vaccine safety: proof-of-concept in the Vaccine Safety Datalink Project. *American journal of epidemiology.* Jan 15 2010;171(2):177-188.
5. Kramarz P, DeStefano F, Gargiullo PM, et al. Does influenza vaccination exacerbate asthma? Analysis of a large cohort of children with asthma. Vaccine Safety Datalink Team. *Archives of family medicine.* Jul 2000;9(7):617-623.
6. Klein NP, Hansen J, Lewis E, et al. Post-marketing safety evaluation of a tetanus toxoid, reduced diphtheria toxoid and 3-component acellular pertussis vaccine administered to a cohort of adolescents in a United States health maintenance organization. *The Pediatric infectious disease journal.* Jul 2010;29(7):613-617.
7. Kulldorff M DR, Kolczak M, et al. A maximized sequential probability ratio test for drug and vaccine safety surveillance. *Sequential Analysis.* 2011;30(1):58-78.
8. Li L, Kulldorff M. A conditional maximized sequential probability ratio test for pharmacovigilance. *Statistics in medicine.* Jan 30 2010;29(2):284-295.
9. Greene SK, Kulldorff M, Yin R, et al. Near real-time vaccine safety surveillance with partially accrued data. *Pharmacoepidemiology and drug safety.* Jun 2011;20(6):583-590.
10. Yih WK, Kulldorff M, Fireman BH, et al. Active surveillance for adverse events: the experience of the Vaccine Safety Datalink project. *Pediatrics.* May 2011;127 Suppl 1:S54-64.