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Executive Summary

Background

The Office of Counterterrorism and Emerging Threats (OCET) within the Food and Drug Administration (FDA) provides strategic leadership and coordination for the FDA's counterterrorism and emerging threat portfolios. It identifies and resolves the complex scientific and regulatory challenges facing the development, approval, availability, and security of Medical Countermeasures (MCM) needed to counter urgent pandemic or terror-related biological or chemical threats to public safety.

In the event of a public health emergency, MCMs—drugs, biologics (e.g., vaccines), and devices (e.g., ventilators, diagnostics)—are used to address chemical, biological, radiological, and nuclear (CBRN) threats. The best MCM available for a CBRN public health response may not be FDA-approved or cleared for use specifically against that threat. To manage this risk, the FDA must actively monitor, in real-time, the incidence of Adverse Events (AE) and relevant health outcomes associated with use of the MCM. Currently, however, systems for reporting AEs have limitations and cause delays in providing relevant safety information to key decision makers.

Study Purpose

OCET seeks to understand how to maximize the use of existing data sources that could advance its risk management capabilities. Existing claims data (the majority of the data captured in existing databases) are standardized and comprehensive. But those data have several key drawbacks: diagnostic codes are error-prone and it has significant temporal limitations. Therefore, OCET engaged The MITRE Corporation—The operator of the CMS Alliance to Modernize Healthcare (CAMH) Federally Funded Research and Development Center (FFRDC)—to assess the feasibility of using near-real-time Electronic Health Record (EHR) data to advance its risk management capabilities.

MITRE designed a study—the Adverse Event Monitoring and Analysis Proof of Concept (AE-MAP) —to determine whether it is feasible to extract safety and effectiveness signal information from EHRs and, if it is, to assess if those data can provide useful information about MCMs. Specifically, MITRE's objectives were to:

1. Advance the FDA's understanding of the possibilities and limitations of using EHR data mining and analytics
2. Identify critical gaps in using the processes and infrastructure of EHR data systems for the stated purpose
3. Assess a process to inform the FDA of any AEs identified during the course of this study

Originally, AE-MAP sought to query data from the entire EHR record. However, after MITRE assessed the state-of-the-art for de-identifying narrative data, MITRE determined that it would be impractical, given the current state of the art, to receive and use de-identified, unstructured data elements. For that reason, MITRE limited AE-MAP to de-identified structured EHR data; unstructured data fields, such as narrative text, were excluded from the data set. AE-MAP focused on influenza-like illness (ILI). MITRE's analysis focused on AEs from both antivirals and vaccines and also considered the effectiveness of the vaccines. Note, however, that the

findings from this study are not intended to provide actual rates, types, or causes of adverse events from use of the influenza vaccine or treatment for influenza.

Data Partnerships

One of MITRE's first steps was to identify an EHR data source. In partnership with OCET and other key federal stakeholders, MITRE developed a set of requirements, a logical data model, and a list of candidate EHR providers. Engaging a data partner proved to be very challenging. A number of factors played into this challenge, including limitations in the scope of the project and reluctance on the part of candidate partners based on perceived or real risks. As a result, AE-MAP engaged one data partner, HealthInfoNet (HIN), the state of Maine's Health Information Exchange (HIE), a system with over 30 hospitals and over 400 private practice providers. EHR data received from all these providers are normalized and updated every 24 hours into a patient-centric EHR format in the HIE. HIN and MITRE entered a collaboration under a Data Use Agreement (DUA) to receive a limited data set of EHR details. MITRE pre-established security and privacy safeguards for the data from HIN (see Appendix A for details). The HIE provided details on age, gender, diagnosis, procedures, laboratory, results, medications, and encounters. The HIE was not able to provide data on vital signs.

Summary of Findings

The overall feasibility findings resulting from examining EHR data indicated that HIN's ***EHR structured data could help to inform a risk assessment based on AE signals***. The structured data analyzed in this study provided information regarding diagnosis, procedures, laboratory results, and medications as well as limited demographics. A key component of this study's success is that HIN has systems to normalize the data it received from its various EHR providers. Normalization is necessary to facilitate analysis, unless a source is identified that uses the same EHR system across all providers of patient EHR data.

A key component to assessing causality is identifying comorbidities and concomitant medications. MITRE determined that ***comorbidity and concomitant medications data could be extracted*** if sufficient historical data, such as medications prescribed to the patient and date of dispensing, is provided by the data source. The data provided by HIN effectively reported any medications prescribed to a patient, including the date of dispensing. MITRE was able to correlate dispensing dates to dates on which diagnosis codes are entered into EHR systems (i.e., encounter dates) as well as the dates comorbidities are diagnosed. Therefore, the structured data provided by HIN, and in the format provided, can inform on treatments (such as antibiotics dispensing) for complications with influenza, treatments associated with underlying conditions that may put someone at high risk for influenza, as well as treatments that may cause and AE potentially attributed to (or contributed by) an influenza infection. MITRE determined that there are limitations to causal analysis related to concomitant medications. The team found it difficult, without access to the complete EHR, to evaluate whether concomitant medications were responsible for the comorbidities observed. The structured data only provided diagnosis codes and diagnosis date, medication name and dispensing date. The care provider's notes were needed to gain more information on the patient's history. ***However, structured data allows signal refinement to an initial level,*** enough to determine from comorbidities and concomitants if patients at risk of an AE can be subcategorized based on other existing conditions, treatments or demographics.

MITRE determined that ***true signal refinement could not be done with the EHR structured data alone***. The team concluded that understanding the details on the patient's record and establish causality would require full access to their record, including unstructured data (e.g., notes, narratives, self-reporting, other data in the record).

MITRE determined that ***even "near-real-time" data has built-in delays***. During the course of the near-real-time data analysis, MITRE found that EHR data gets populated over the course of several days post-encounter: laboratory results information is added over time; diagnosis and procedures codes can be added and modified after encounter information is processed to collect insurance payment. However, medications data is typically entered closer to the encounter date, allowing a temporal marker for AE monitoring. Real-time data analysis in the future should employ ongoing follow-up retrospective analysis to consistently identify corrections and changes in diagnosis, procedures, and laboratory results as data continues to filter into EHR records.

MITRE found that ***automation has its limits at this time***. Data extraction algorithms can be automated to direct data for analysis into a database able to receive daily updates. However, a human in the loop is needed to run the algorithms for data analysis and to interpret results.

AE-MAP's retrospective study, which included EHRs across multiple years, reveal an increasing capture of vaccine information by HIN systems. This increase indicates that the ***mechanisms required to effectively monitor vaccine inoculation are increasingly in place***. ***MITRE determined that it was feasible to detect severe AEs, while less severe AEs were likely to be underreported.*** Sufficient volumes of vaccination data were gathered to conduct a safety analysis. This analysis, however must be caveated by a critical point: As the AEs for vaccines typically are mild in nature they are unlikely to be significantly reported in EHRs the way they would be in a controlled clinical study which relies on patient self-reporting of AEs. For most mild to even moderate AEs occurring with marketed use of the product, patients will often forgo reporting mild symptoms to a clinician for EHR documentation. MITRE observed significant discrepancy between the vaccine clinical trials (as labeled) and population incidence observed during the course of AE-MAP. Mild symptoms, most commonly reported AEs in trials, typically are not reported during marketed use of products and do not result in a treatment response or, if reported, may be consigned to narrative data-fields (e.g., minor swelling at site of vaccination is unlikely to require medical intervention yet be documented in a narrative). This logic does not extend toward more severe AEs, where the level of severity is directly proportional to the probability of it being reported in an EHR. For antivirals, the incidence of severe AEs was effectively monitored, to the extent of triggering false-positives due to comorbid or concomitant confounders. The fact that severe AEs are more likely to be reported and detected suggests a positive feature for of utilizing EHR data for near-real-time signal detection.

Due to insufficient capture of EHR data on vaccination combined with results from influenza testing to generate vaccine effectiveness rates with statistical power, ***MITRE was unable to conduct a comprehensive vaccine effectiveness assessment*** based on the HIN's EHR data. Nevertheless, MITRE was ***able to detect incidence of breakthrough influenza infection***, which can provide an indication of vaccine effectiveness. MITRE showed effectiveness of influenza vaccines to be at 45% for 2012-13 season and 40% for 2013-2014 season while vaccine labels reported vaccine efficacy at 60% against matched influenza strains, and 42% against unmatched strains.

Regarding the results from EHR data analyses, MITRE conducted a retrospective study prior to exercises in real-time to generate a baseline of historic data for AE-MAP on antiviral safety, vaccine safety (monitoring for the incidence of AE tied to usage), and vaccine effectiveness, (attempting to gauge the rate of breakthrough infection post-vaccination). MITRE analyzed EHR data from HealthInfoNet on influenza seasons 2011-12, 2012-13 and 2013-14 for the retrospective study.

While examining antiviral usage, a combination of IDC-9 and LOINC codes pointed to initial signals indicating cases of arrhythmia, congestive heath failure, gastrointestinal bleeding, leukopenia, liver failure, nausea & vomiting, renal failure, stroke and thrombocytopenia in patients prescribed approved influenza antivirals. Initial signal refinement, considering comorbidities and other medications prescribed, indicated that perhaps only nausea & vomiting and arrhythmia AE could be associated to influenza antiviral use; however, additional signal refinement, outside the scope of AE-MAP, would be required to validate the emergence of other AEs.

The monitoring of approved influenza vaccine dispensing resulted in only two AEs identifiable in the retrospective data: swelling at site of injection and fatigue & malaise. The frequency of AEs found in EHRs for antivirals and vaccines was lower than the frequency recorded in clinical studies. Furthermore, MITRE found preexisting conditions and medications in the EHRs data which may have contributed to the low frequency of fatigue & malaise measured and reported post initial signal refinement.

In terms of results on influenza infection post vaccination, MITRE measured vaccine effectiveness and the results showed that overall, there is insufficient capture of data on vaccination combined with results from influenza testing to generate vaccine effectiveness rates with statistical power. However, as noted above, MITRE showed effectiveness of influenza vaccines to be at 45% for 2012-13 season and 40% for 2013-2014 season while vaccine labels reported vaccine efficacy at 60% against matched influenza strains, and 42% against unmatched strains.

Subsequent to the retrospective study, MITRE initiated a second analysis of EHR data, this time in real-time. The data analysis runs covered in real-time in this study examined data from EHRs refreshed every 24 hours. MITRE conducted real-time analysis of data during December 2014 and January 2015. The total volume of patients receiving antivirals or vaccine in that period was very low. MITRE only found sporadic patients with ICD-9, ICD-10, or LOINC codes suggesting AEs such as liver dysfunction, anemia or nausea & vomiting in patients receiving antiviral while no AE data was captured for patients receiving flu vaccines during that period. A signal triggered by congestive heart failure diagnoses in records from patients receiving an antiviral was determined to be a false positive. Vaccine effectiveness was not measurable in real-time due to the low volume of patients showing influenza test results in their record.

Based on these findings, MITRE concludes that ***structured data fields within EHRs offer sufficient data to monitor and assess the safety, and possibly effectiveness, of MCM use in a population and that this information can be extracted and analyzed in near-real-time***. The data necessary to conduct signal detection and early-stage refinement for multiple types of analyses exist within structured EHR data-fields, and this data can be accessed and assessed in a near-real-time capacity. When looking to expand these findings into broader relevance, given the diversity of EHR platforms available within the United States, it may be crucial to next assess, within

representative EHR systems, the overall quality and integrity of what is considered structured data. These findings would then have to be mapped to the data elements suggested by AE-MAP to be sufficient to evaluate AE signals.

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1. Background

The U.S. Food and Drug Administration (FDA) is charged with protecting the public's health by ensuring the safety, security, and efficacy of human and veterinary drugs, biological products, medical devices, the nation's food supply, cosmetics, and any products that emit radiation. The FDA is also responsible for advancing public health by helping speed innovations that make medicines and foods more effective, safe, and affordable, and by helping the public receive the accurate, science-based information it needs to use medicines and foods to improve its health. [1]

Within the FDA, the Office of Counterterrorism and Emerging Threats (OCET) provides strategic leadership and coordination for the FDA's counterterrorism and emerging threat portfolios by identifying and resolving the complex scientific and regulatory challenges facing the research, development, approval, availability, and security of Medical Countermeasures (MCM) needed to counter urgent pandemic or terror-related biological or chemical threats to public safety. [2]

In the event of a public health emergency, MCMs—drugs, biologics (e.g., vaccines), and devices (e.g., ventilators, diagnostics)—are used to address chemical, biological, radiological, and nuclear (CBRN) threats. The best MCM available for a CBRN public health response may not be cleared for used against that threat. For example, some products may have been approved based on their demonstrated efficacy in animals and thus have limited human data. Other products may be marketed, but not yet approved or cleared for the emergency use. Others may be unapproved for marketing for any use.

As a result, administering MCMs during a public health emergency, while necessary, may expose patients to an increased risk of adverse events (AE). This increased risk could stem from increased use (exposing more patients to previously known risks), from use of an approved product for an unapproved use, or from the absence of the robust safety and efficacy data set that medical products normally accumulate during rigorous pre-market clinical trials. As a result, previously undocumented AEs may arise in the course of treatment. To manage this risk, AEs and relevant health outcomes associated with MCMs must be actively monitored. Currently, however, systems for reporting AEs have limitations and delays in providing relevant safety information to key decision makers.

FDA has explored, and continues to explore, sources of information that could augment the existing AE reporting systems, including the FDA's Mini-Sentinel. Mini-Sentinel allows FDA to assess risks associated with medical products. [3] However, the majority of data within the system relies on claims data, the standardized, formatted data derived from bills submitted by physicians, hospitals, and other providers paid by commercial and government health plans. While claims data has several benefits, such as standardized coding, rich patient information, it has limitations for assessing the safety and effectiveness of MCMs during an emergency. For example, diagnostic codes, though included in claims data, are often inaccurate reflections of actual disease states and the information is not timely and fails to convey a patient's history (e.g., confounding factors such as comorbid conditions and concomitant medication usage).

FDA is working to improve its capabilities to assess the risks and benefits associated with MCM use in near-real-time. The FDA engaged The MITRE Corporation to conduct a proof of concept

to determine the feasibility of using EHR systems to conduct near-real-time monitoring of health outcomes—including serious or unexpected AEs—associated with MCMs during public health emergencies. FDA engaged MITRE to assess whether EHR systems have the potential to manage risks associated with the use of MCMs as a reliable data source that allows surveillance of high-quality, real-time data that provides patient history, encounter, diagnosis, and treatment information across a large, diverse population.

1.1 Purpose and Scope of Study

The proof of concept's purpose is to determine the feasibility of using EHRs to advance the FDA's ability to manage risks related to MCMs during a public health emergency.

Certain elements of the analysis and certain realities of the overall surveillance landscape impacted the feasibility study's options.

- **Standard Operations.** The study looked to determine whether typical EHR data capture protocols followed and whether current EHR systems provided adequate means for sufficient data access and signal clues.
- **Structured EHR Data Only.** Although the study aimed to address the feasibility of querying all EHR data, due to the technical inability to presently de-identify unstructured data elements within an EHR, the feasibility study was constrained to structured EHR data-fields.
- **Patient Privacy.** Maintaining the privacy of patients is of paramount importance, so all EHR data in this study was provided to MITRE de-identified.

To fulfill the purpose of the study, the MITRE team set out to conduct near-real-time monitoring of existing, large EHR systems in order to establish whether the safety and effectiveness of MCMs could be determined from EHR data analysis. This study focused on seasonal influenza as the initial model as a proxy for a pandemic influenza public health emergency and on antivirals and vaccines for influenza as the initial model for the MCMs. Note, however, that the findings from this study are not intended to provide actual rates, types, or causes of adverse events from use of the influenza vaccine or treatment for influenza.

MITRE's objectives during this study were to:

1. Advance the FDA's understanding of the possibilities and limitations of EHR data mining and analytics
2. Identify critical gaps in the processes and infrastructure of EHR data systems for the stated purpose
3. Assess a process to inform the FDA of any AEs identified during the course of this study

The information gathered during this study may be used to inform additional feasibility studies or future approaches for enhancing MCM data collection during a public health emergency.

1.2 Process

To determine whether EHRs can be used to enhance the FDA's ability to manage the risks related to MCMs, MITRE proposed answering the following questions:

1. Can agreements for adequate EHR data provision be established?
2. Can sufficient EHR data be provided in a timeframe that permits signal detection?
3. Can signals be detected in an EHR data set?
4. If signal detection is possible, can those signals be detected in an ongoing, near-real-time assessment of EHR data?
5. What would need to be done to be ready to use EHRs to advance risk management during a public health emergency?

To address these questions, MITRE did the following:

- Identified suitable EHR data partners and established data use agreements necessary to access EHR data
- Created a data analytical environment at MITRE for the EHR data
- Developed the data element processing requirements for executing the data analysis
- Executed all data queries and statistical analyses
- Generated a summary of the results of statistical analyses and provided weekly reports of these results to OCET

In addition, OCET and MITRE formed a Steering Committee to provide advice and guidance throughout the study (refer to Appendix L).

2. Feasibility Findings

2.1 Accessing Electronic Health Record Data

The following sections summarize MITRE's approach and results in recruiting an EHR data partner and establishing the data-use agreement for the Adverse Event Monitoring and Analysis Proof of Concept (AE-MAP). It also provides insights and recommendations for future EHR data-analysis projects. Note, however, that these sections do not constitute legal advice.

Refer to Appendix H and Appendix I for details regarding database querying and statistical analysis methodologies.

2.1.1 Identifying a Data Partner

MITRE conducted an extensive outreach effort to identify, engage, and recruit data partners for this initiative. In partnership with OCET and other key federal stakeholders, MITRE developed a set of requirements and a list of candidate EHR providers.

MITRE established the following high-level requirements (see Table 1) to determine suitability of potential partners. Such criteria may be applicable to future efforts:

Table 1. Data Partner Requirements

#	Requirement	Description
1	Technical Capability	The provider must possess the in-house technical proficiency to facilitate data compilation and extraction.
2	Near-Real-Time	The provider must have an EHR system that is advanced enough to support real-time, or near-real-time, data analysis.
3	Generalizability	The provider's EHR system must possess sufficient data to have broader applicability in the U.S. healthcare domain.
4	Statistical Relevance	The provider must have a patient population of sufficient demographic and geographic diversity to allow for sufficient statistical rigor.
5	Bandwidth	The provider must be willing to devote the internal resources necessary to ensure the success of AE-MAP.
6	Data Types	The provider must be able to provide identified data elements, such as patient age or admission or service date, key to conducting signal preparation analysis. (See Appendix E. for detailed description of data requirements.)
7	Privacy	The provider must be able to de-identify data so that the identity of individual patients cannot be determined during the analysis.

MITRE considered EHR data providers from a variety of sectors:

- Private healthcare providers, including hospitals and larger healthcare systems
- United States Government (USG)
- Health Information Exchanges (HIE)
- EHR software vendors

- Medical institutions with academic affiliations

Although many health care providers that generate and collect EHRs exist within these categories, engaging a data partner proved to be very challenging. A number of factors played into this challenge, including the ability of potential partners to meet the data set requirements, the length of time required to establish an agreement, the reluctance of potential partners to engage in a data sharing agreement due to perceived or real risks, differing research priorities, concerns about handling and use of data, and the opportunity cost of participating in this study.

Appendix D. includes a detailed descriptive table of the data partners with which MITRE engaged and the outcomes of the engagement. Over the course of many meetings, discussions, and email exchanges, MITRE reached a series of high-level determinations regarding data partners that are expanded upon in Section 2.1.2 below.

Additionally, after a six-month process of outreach, meetings, and negotiations, the team identified an HIE willing to provide near-real-time data (24-hour delay) that met the proof of concept's requirements.

2.1.1.1 AE-MAP's Data Partner

HealthInfoNet, a non-profit HIE located in Portland, Maine, was selected as the partner for AE-MAP. Although it is limited geographically to only the state of Maine, this HIE has access to 88 hospitals, over 400 private practice providers, and more than 1.2 million patients.

HIN receives most patient data as HL7 messages. These messages are converted and transformed into data elements that populate a patient-centric EHR data warehouse. The normalized patient data is updated every 24 hours, making HIN a suitable data provider for near-real-time EHR data analysis.

MITRE shared the key elements that would need to be extracted (referred to as the Logical Data Model [LDM], Appendix E.). HealthInfoNet and MITRE finalized a Data Use Agreement (DUA) to receive a limited EHR data set.

MITRE and HIN established a two-phased approach:

- **Retrospective analysis.** During the first phase, HIN provided retrospective data that covered the previous three flu seasons (August 2011 to June 2014). During this phase, MITRE used the retrospective data to generate a baseline and refine its analytical approach.
- **Near-real-time analysis.** During the second phase, MITRE received daily EHRs (structured data only) during December 2014 and January 2015 to conduct the real-time data analysis and feasibility studies set as goals for AE-MAP.

For both phases, HIN provided de-identified data with a unique identifier per patient. The unique identifier's key was retained by HIN. HIN also provided the patients' gender and age, original dates of encounters, diagnosis, procedures, and medications dispensing details. The HIE was not able to provide data on vital signs.

2.1.2 Accessing Electronic Health Records Data—Findings, Lessons Learned, and Recommendations

The following are lessons learned and recommendations regarding accessing data for future signal detection exercises.

- HIEs as data intermediaries: HIEs can be important intermediaries, as they have already undertaken the arduous task of unifying and standardizing (normalizing) data across providers and are generally oriented toward external research and partnerships.
    - An HIE can provide data from hospitals and private practices. However, the HIE must have the systems and expertise to normalize data from the hospitals and private practices, since data from these sources do not originate from a common EHR system. It takes a significant amount of effort for an HIE to create systems that efficiently normalize data from multiple providers to a patient-centric EHR. During the AE-MAP, MITRE used an HIE that normalized data in 24-hour cycles.
- EHR vendors: Many EHR vendors primarily offer on-site EHR installations, where the data is housed locally with the provider and inaccessible to the EHR vendor. Even vendors who offer remote or cloud storage of EHR data are constrained by not owning the rights to the data.
- Healthcare providers with "homegrown" EHR systems: These systems are so heavily customized to the individual provider that methods developed for it could not be easily applied toward other EHRs.
- Large healthcare systems and teaching hospitals: MITRE found a range of EHR systems-ranging from leading vendors to "homegrown." Although these partners are typically more amenable to research-partnerships, competing internal priorities may limit their willingness to participate in future efforts.
- USG agencies remain potential high-value partners: Although AE-MAP was unable to establish a collaboration with a USG agency such as VHA or DoD, MITRE believes that USG agencies remain potential high-value data partners for signal detection for the following reasons:
    - Existing ability to monitor for AE signals within their existing EHR systems.
    - Common interest in monitoring, detecting, and sharing both AE information and signal detection techniques.
    - Future efforts to access unstructured EHR data may require other legal agreements such as a Business Associate Agreement (BAA), a contract that protects personal health information (PHI) in accordance with HIPAA guidelines.
    - In the future, if signal detection work is extended to EHRs' non-structured data, a BAA may be required because PHI information may appear in the text fields. A BAA might be needed to address potential PHI concerns.
- Small providers may need additional support: Smaller providers may lack the internal technical and legal expertise necessary to enter into data sharing arrangements. In order to access their information, more technical guidance and a supportive regulatory

framework (e.g., EHR incentive programs, Meaningful Use funding) may need to be established.

- Risks of sharing may deter potential partners: Future providers may be hesitant to share even de-identified data with third parties due to a lack of compelling incentives to share data and the ever-present risk of data breaches.
- Resource availability can constrain participation: Providers need available internal resources (e.g., staff) prioritized for such data sharing collaborations as well as compensation for costs incurred.
- Data structure and governance are key enablers: Future data providers must have structured their data, and have the proper data governance in place, in order to enable population-level analyses that can query their entire patient population simultaneously and not just query data from individual patients.
- Incentives may be critical to enable population-level signal detection: Establishing widespread EHR data partnerships with private industry to promote robust population-level AE signal detection may require incentives.
- EHR systems vary widely: There is a large gradient in terms of EHR systems and capabilities across providers, and even EHR systems from the same company can be highly customized across providers.
- Extensive research would be required for development: Developing the algorithms architecture requires upfront planning and research to develop the proper tables of data for querying. These tables for querying list the diagnosis codes, procedure codes, laboratory results codes and medications names of relevance to identify AEs of interest. Acquiring and organizing all this information requires a significant amount of time and effort before monitoring can begin.
- Table revisions are required over time: Tables for querying should be subjected to revisions over time to identify noise data, which can generate an unnecessary level of false positives.
- Retrospective analysis is required for real-time: Real-time data monitoring requires follow-up retrospective monitoring to account for late data additions (data back-fills), modifications, and corrections post-initial patient encounter as well as corrections for data delays due to potential servers being down or interruptions of service.
- Skillset requirements for establishing the environment: Expertise in database administration, biostatistics, and programming are essential skills to include in future data analysis exercises relying on EHRs data.
- Data partners require expertise: A data source with clinical expertise, or a data source in collaboration with a third party with clinical expertise, is crucial to develop the algorithm's architecture needed to effectively exploit the structured data elements in EHRs.
- Data partners must properly de-identify data: Data from a provider (e.g., clinic or hospital) must be properly de-identified prior to use; this will require a provider who is skilled and knowledgeable in de-identifying and exporting EHR data.

- Two approaches can be taken to analyzing data from different providers: Sourcing data from multiple data providers will require the additional challenge of unifying the results. Two approaches may be used. The first approach requires standardizing the data from multiple sources into a unified dataset before running the analysis. The second approach requires developing customized analyses for each dataset and summarizing results. Both approaches risk significant data loss and improper interpretation of results.
- Working within the data partners' environment can simplify the analysis: Developing the algorithm's architecture inside the main data repository (e.g., the HIE) provides access to more data without transferring data to a third party. Working with a third party introduces data availability delays. It requires careful planning to create a process that can regenerate the data source's database inside the third-party environment.
- Simplify data access: Future analyses should occur as close to where the primary EHR databases are maintained as possible (preferably avoiding having to store the data with intermediaries). This will reduce potential issues arising from transmission and data loss due to transferring data from one environment to another.
- Monitoring for data accuracy: If data for future monitoring efforts will be housed away from the provider, run a comparative inventory to ensure that the transfer process does not erode the data.
- Large sample sizes are required: Future analytic efforts should access large population samples to establish statistical rigor.
- Diversity in demographics and geography is required: Future analytic efforts should recruit data partners who, either in totality or individually, possess sufficient diversity in patient demographics and geographic spread to ensure a comprehensive and unbiased sampling.
- Clinical expertise is required: Clinical expertise by those performing the analysis is crucial to develop the algorithms architecture needed to effectively exploit the structured data elements in EHRs.
- Data partners must have the capability to mine data across patients: A data source with a pre-existing architecture of algorithms able to harvest population data that collects elements such as diagnosis codes, procedure codes, laboratory results values, and potential vital signs must be in place (i.e., prior to the emergency) must be available.
- Data sources must be able to input custom and evolving search criteria: A data source must be in place with a system that can easily incorporate reference tables that list diagnosis, procedure, laboratory codes (including code descriptions), and laboratory results values relevant to the emergency.
- Consider including reference tables provided by an external source or transcribing the reference information into internal tables.
- Once in the system, adapt the reference tables to the emergency and as information about the emergency evolves.
- The ability to screen for comorbidities is important: A data source must be in place with a system that can incorporate reference tables listing comorbidities for the population.

- The ability to screen for concomitants is important: A data source must be in place with a system that can incorporate reference tables listing other medications (concomitants) for the population.
- Data sources must draw data from additional tables: A data source must be in place with a system that can incorporate reference tables with other diagnosis, procedures, and vital signs codes that provide auxiliary data points.
- Data sources must conduct population-level statistics: A data source with EHR systems vetted to provide population-level, structured, EHR data elements that can inform AE signal evaluation must be in place.
- Data sources must be expansive enough to collect vaccine data on patients: A data source with EHR systems vetted to provide population-level, structured, EHR data elements sufficient to inform vaccination date and influenza test results must be in place.
- Data sources capable of conducting internal analytics can simplify agreements: Establishing arrangements with a data source that can execute and provide population-aggregated data on AE signals and vaccine effectiveness may avoid delays in use data agreements.
- Data partners may have a diverse set of EHRs, each boasting different capabilities: Considering the significant proliferation of EHR systems in the United States in the last five years and the existing EHR systems diversity, it may be crucial to assess the overall quality and integrity of the structured data within representative EHR systems; this relative to providing sufficient data elements to evaluate AE signals. For example, data from sources who receive third-party updates may not receive updates in real-time frequency or may not receive updates with the granularity needed for signal assessment (e.g., system may not receive data from all medication dispensing instances for a patient).
- Developing the algorithms architecture inside the main data repository (e.g., HIE) provides access to more data and without the rigors of data transfer to a third party. The latter introduces data availability delays and requires careful planning to create a process that can regenerate the data source's database inside the third-party environment.
- The analysis should occur close to the databases' location. This will reduce issues arising from transmission and data loss.
- Making pre-arrangements with a data source that can execute and provide population-aggregated data on AE signals and vaccine effectiveness may avoid delays in establishing data use agreements.
- Considering the significant proliferation of EHR systems within the United States, it may be crucial to next assess, within representative EHR systems, the overall quality and integrity of what is considered structured data. These findings would then have to be mapped to the data elements shown by AE-MAP to be sufficient to evaluate AE signals. For example, data from sources that receive updates from third parties may not receive updates in real-time or may not receive updates with the granularity needed for signal assessment (e.g., system may not receive data from all medication dispensing instances for a patient).

2.2 Detecting Signals in Electronic Health Records

Once HIN sent the data, MITRE started its analysis to determine if AE and effectiveness signals could be found. This section presents an overview of MITRE's analytical findings.

2.2.1 Electronic Health Record Data Elements

With the exception of vital signs (e.g., temperature), HIN's EHRs captured all of the data elements within the LDM. Measures of temperature and weight were captured via diagnostic codes for fever and obesity, respectively. In addition, HIN data captured some patient immunization vaccine information not included within the LDM.

2.2.1.1 Medication Data

The data provided by HIN includes any medication prescribed to a patient and the date of dispensing. MITRE was able to correlate dispensing dates to the diagnosis dates for diagnosis codes and diagnosis dates for comorbidities. Therefore, the format and structured data provided by HIN can inform on treatments (e.g., antibiotic dispensing) for complications associated with influenza, treatments associated with underlying conditions that may put someone at high risk for influenza, and treatments that may cause an AE that is potentially attributed (or contributed) to influenza infection. The last treatment category can include chemotherapy drugs, neuropsychiatric drugs, renal failure drugs, and non-steroidal anti-inflammatory drugs.

MITRE did not find the regimen prescribed for both antivirals, so MITRE monitored concomitant medications and, for analysis purposes, assumed that the regimen was according to the indication in the product label. Initially, MITRE planned to use the National Drug Code (NDC) to follow the medications used by patients. However, during the analysis, MITRE learned that the NDC is very irregular within the data because systems lack conformity across the NDC users and providers. Instead, MITRE leveraged key-word searches for drug names (both generic and branded terms) for search queries.

2.2.1.2 Procedure Data

The procedure codes monitored in this study were extracted from the code list for gastrointestinal bleeding and respiratory failure AEs. These included only codes for blood transfusion, intubation, and respiratory assistance with a ventilator. MITRE did not find any patients who had these codes in the retrospective analysis data.

This study determined that the data supported the monitoring for these codes. The absence of any records containing these codes indicated that there were no instances of blood transfusion, intubation, and respiratory assistance with a ventilator associated with influenza during this study.

2.2.1.3 Laboratory Results Data

Flu testing information and flu test results were extracted from the HIN laboratory results table. The analysis used LOINC codes to cover approximately 400 tests in the U.S. market. A binary test result of positive/negative did not allow a measure of the accuracy of the tests. The team specifically used the HL7 abnormality indicators A, H, and HH to identify positive test results. The analysis assumed that N and Null were indicators of negative flu test results in the

abnormality column of the lab results table provided by HIN. Laboratory results were also used to indicate AEs. The results were counted when a test was included in the record at the time of MCM dispensing. They were then assessed with a "human in the loop" to determine if the result value or the HL7 abnormality indicator was severe enough to correlate to an AE initial signal.

2.2.1.4 Diagnosis Data

A diagnosis table provided the necessary ICD-9 and ICD-10 codes to ascertain a patient's diagnoses. This table was used to identify influenza and AEs.

2.2.1.5 Additional Data

Secondary data tables, including "Encounter" and "Demographics," provided supporting information that was not directly tied to the analysis. This data can provide additional contextual information.

One element included in the HIN model, but excluded from the LDM, was a patient immunizations table, which documents a patient's immunization history. This data could prove valuable as an additional information source to identify whether a patient was immunized for influenza. However, HIN's table was derived from self-reported data (making information like date of inoculation suspect), and provided limited vaccine details (e.g., name and type of vaccine were not included). Thus, the immunization table was excluded from the analysis.

2.2.2 Lessons Learned and Recommendations for Using Electronic Health Record Data to Assess Adverse Events and Vaccine Effectiveness

The following are lessons learned from using EHR data to assess AEs and vaccine effectiveness. They summarize MITRE's recommendations for future signal detection exercises that rely on structured data fields.

- Structured data provided insights into patient context and therapeutic approach. MITRE was able to analyze the structured data to understand the patient context, illuminating both underlying conditions that may put a patient at increased risk for influenza and complications that may have arisen due to influenza (such as pneumonia). The medication data helped to identify treatments that may cause AEs that match those associated with influenza itself.
- Medication is best tracked by name, not code. Medication data was collected using both generic and branded medication names and not NDCs. This avoided the diversity and lack of uniformity in NDCs from the data providers sending information to HIN. Real-time data analysis can accurately include medications data if the medication's name is used in the queries to extract data. Medication name and dispensing date were then correlated to diagnosis and encounter dates and diagnosis codes.
- There is little overlap between vaccination data and flu-test data. The overlap between records data on vaccination and corresponding influenza laboratory test results was less than 10% of the data available from HIN. The vast majority of the influenza laboratory test results could not be correlated to a vaccination in a patient's record, reducing MITRE's ability to calculate vaccine effectiveness. Real-time data analyses for vaccine

effectiveness may require additional protocols inside the data source to capture the vaccine information in the patient's record for any patient receiving an influenza test.

- Limited vaccine effectiveness analysis can be conducted. An indication of vaccine effectiveness can be ascertained by analyzing data made available by HIN. This data combines vaccine dispensing data from the medications data provided by a source and, in the case of influenza vaccine effectiveness, the data from influenza laboratory test results. Tables for querying include the list of laboratory tests available (with the proper codes) and the names of the vaccines of interest.
- Unifying patient identifiers allowed for longitudinal patient tracking. The analysis of EHR data from HIN systems allowed MITRE to follow any patient across time, and through different providers, using a unique patient linkID. This was a unique patient identifier existing in the system developed by HIN. The linkID is always connected to an encounter (this includes encounter type, such as inpatient or outpatient), and to any diagnosis, procedures, laboratory results, and patient demographics (e.g., gender, age)
    - From the medication table, linkID, medication name and dose, and dispensing date were sufficient to execute the data analysis. (NDCs were provided by HIN but were not used in the course of this study.)
    - From the diagnosis table, diagnosis ID, linkID, encounter ID, diagnosis code, diagnosis order, and diagnosis code description were sufficient to execute data analysis.
    - From the procedures table, procedure ID, linkID, encounter ID, procedure order, and procedure description were sufficient to execute data analysis.
    - From the results table, linkID, encounter ID, category, subcategory, test name, LOINC, abnormality (HL7 indicator), observation date/time, result value, result reference, and result unit were sufficient to execute data analysis.
- Numerous data elements are associated with influenza. Structured data from HIN clearly informed on treatments (such as antibiotics dispensing) for complications with influenza, treatments associated with underlying conditions that may put someone at high risk for influenza, as well as treatments that may cause an AE potentially attributed to (or contributed by) an influenza infection.
- Comorbidity data was accessible. Comorbidity data, including pregnancy, was available from the diagnosis and procedures tables and identifiable by diagnosis and procedure codes (ICD-9, ICD-10, and CPT). HIN providers are migrating to ICD-10 at different rates; however, historical data on diagnosis and procedures is preserved as ICD-9 and CPT codes.
- Concomitant data was accessible. Concomitant medications were extractable by querying patient history longitudinally using medication names.
- Concomitant data is of limited use without care provider notes. MITRE found it difficult to evaluate if concomitants were responsible for the comorbidities observed. This was difficult to assess without access to the complete EHR. The structured data only provided diagnosis codes and diagnosis date, medication name, and dispensing date. The care provider notes were needed to gain more information on the patient's history.

- Data from radiology images may need to be excluded. Data from radiology results such as images could not be used if the images contain embedded personally identifiable information.
- LDMs should be similar across partners. The LDM organization should be similar across potential data providers. However, if choosing a data source with multiple data providers (e.g., HIE), it is important to know if the data provider can normalize their data. If data is not normalized, the analysis will be difficult.
- LDM structured data is sufficient for signal detection. MITRE determined that EHR structured data for diagnosis, procedures, laboratory results, medications, and limited demographics is sufficient to inform a risk assessment based on signals for AEs.
- Historical data is needed to identify concomitants and comorbidities. MITRE determined that future efforts can capture comorbidity and concomitant data if the data source provides sufficient historical data.
- Comprehensive signal refinement requires access to unstructured data. MITRE determined that necessary data is probably contained in the unstructured data not tested in AE-MAP (in particular, data to connect medication dispensing rationale such as refills and dispensing in the absence of a diagnosis code). Signal refinement may need to access this data, so it would need a framework to access the identified data. MITRE determined that true signal refinement would require full access to the patient's record, including unstructured data (i.e., notes, narratives, and self-reporting), to understand the details on the patient's record and to establish causality.
- Future efforts can still conduct initial refinement with structured data. Structured data allows signal refinement to an initial level. It provides enough information to determine from comorbidities and concomitants if patients at risk of an AE can be subcategorized based on other existing conditions, treatments, or demographics.
- Future efforts can increase demographic data elements. The MITRE study only included age and gender; other demographics (e.g., race, ethnicity, and zip code) should be considered in future studies using broader populations.
- Future efforts can include vitals data. The MITRE study did not use vital signs data. This data was not available. Future studies may need to rely on vital signs data (e.g., blood pressure) to indicate AEs. Temperature details may be important to indicate an AE, if temperature is not captured as a fever diagnosis.
- Look at various sources for comorbidities in the data. Pregnancy and obesity details may be captured under vital signs or diagnosis, depending of the data source. The data source for the AE-MAP captured this data under diagnosis.
- In the near term, some automation is possible for future analytics, but human intervention will be required. Data extraction algorithms can be automated to direct data for analysis to a database. This was the path MITRE developed with HIN. However, a human in the loop is needed to run the algorithms for data analysis and to interpret the results.
- Longer-term, complete automation of initial signal detection is possible. In the future, and by learning about different MCMs and the expected and unexpected AEs signal their

use generate in EHR data, MITRE can begin to imagine automated systems to indicate initial signals. More data is needed on which AE indicators from the EHRs are most valuable (e.g., lab results, diagnosis codes, procedure codes, and self-reported data).

- Data backfills will require ongoing retrospective sweeps during real-time assessments. Real-time data assessment from EHRs will be affected by data backfills (i.e., corrections and additions), due to the inherent process of patient insurance coverage evaluations.
- Signals may only be detected across data partners. A third party administering the overall effort should run complementary signal-detection calculations on the results received across data partners to determine if a signal exists in aggregate.
- A well-populated knowledge database requires a significant level of research on AEs and associated complications. Future studies should include sufficient time and proper expertise to generate the details for the knowledge database. The combination of a well-crafted knowledge database and iteratively developed queries and business rules is essential for populating the data warehouse containing the patient's relevant data needed to assess the signals and properly report on the signal findings.

2.2.3 Near-Real-Time Data Analysis of Electronic Health Record Data, Overview, Lessons, and Recommendations

MITRE held a real-time signal detection exercise, monitoring EHR data daily for the emergence of signals. The following are lessons learned and recommendations for conducting real-time signal detection exercises.

2.2.3.1 Lesson Learned from Conducting Near-Real-time Signal Detection

This section captures the findings from the daily analyses of the real-time data from HIN and discusses the feasibility of daily data transfers, sufficiency of EHR details, and data volume issues. It also provides recommendations for future exercises.

- Data enters an EHR at different intervals. It takes several days to populate EHR data post-encounter. Information about laboratory results is added over time. In addition, diagnosis and procedures codes are added and modified after the encounter information is processed in order to collect insurance payment. However, medications data is typically entered closer to the encounter date.
- Retrospective reviews of previously scanned data are necessary to monitor for backfill. Real-time data analysis in the future should consider a follow-up retrospective analysis to identify corrections and changes in diagnosis, procedures, and laboratory results.
- Real-time analysis of comorbidities and concomitants necessitates a retrospective analysis. Ascertaining comorbidities and concomitants in real-time analyses requires additional access to historical data for each patient, since indications of pre-existing conditions and medications may only be documented on previous encounters.

3. Retrospective Analytical Results

3.1 Summary of ILI Results for the Influenza Season 2012 – 2013

MITRE used the CDC recommended ILI codes list [5] to retrospectively analyze the frequency of ILI codes usage in the patient population from HIN during the season of 2012 to 2013 when the dispensing of Tamiflu showed a significant peak. The analysis included all patients with encounters between September 2012 and May 2013. MITRE found 198,228 patient with an ILI code in their EHR. Only 19,533 patients from the 198,228 total had a code of the Pneumonia and Influenza (P&I) subset; of those, 4,879 patients received an influenza infection diagnosis code In terms of ILI code usage across the HIN healthcare community during that influenza season, pneumonia (486) was the predominant P&I code followed by influenza diagnoses (codes 487.1, 487.8 and 487 in that order). Only 1,712 patients from the 7,911 dispensed a flu antiviral between September 2012 and May 2013 had an ILI code. Most of the ILI codes used during that period and from the total of 198,228 were to diagnose cough, asthma, upper respiratory infections, pharyngitis, otitis media, pneumonia, bronchitis, fever, sinusitis and chronic bronchitis in that order.

In summary, ILI codes cannot be correlated to the dispensing of antivirals. Most patients (close to 80%) receiving an antiviral did not have an associated ILI code in the structured sections of their EHR. It is possible that narrative in the record is capturing the diagnosis code to dispense an antiviral unless the antiviral was largely prescribed as a preventive measure during that season.

3.2 Vaccine Safety and Effectiveness

3.2.1 Vaccine Dispensing

The following summarizes the data regarding the vaccine dispensing captured by HIN over the course of the retrospective period of assessment.

Table 2. Vaccines Dispensed per Flu Season

	Vaccine Doses						
Flu Season	**Afluria**	**Fluarix**	**FluLaval**	**FluMist**	**Fluvirin**	**Fluzone**	**Grand Total**
Aug 2011–Jun 2012	6,685	2	21	4	4,098	7,285	18,095
Aug 2012–Jun 2013	14,079	2	7	17	17,465	25,724	57,294
Aug 2013–Jun 2014	15,251	836	1,078	35	11,381	21,313	49,894
Grand Total	36,015	840	1,106	56	32,944	54,322	125,283

Note that the dispensing data for the last two flu seasons showed a dramatic difference compared to the first flu season. In reviewing these results with Maine's HIN, MITRE confirmed that the increase in observed vaccinations reflects improvements on the data ***capture*** capabilities by HIN, rather than an actual increase in vaccination.

This finding is significant for AE-MAP. It indicates that EHR data can accurately capture an increasing number of vaccinations if sufficient detail is available to enable safety and effectiveness monitoring. **Note that while it is impossible to determine the precise number of vaccinations captured by the EHRs, the available information is sufficient to enable statistically rigorous explorations of safety and effectiveness.**

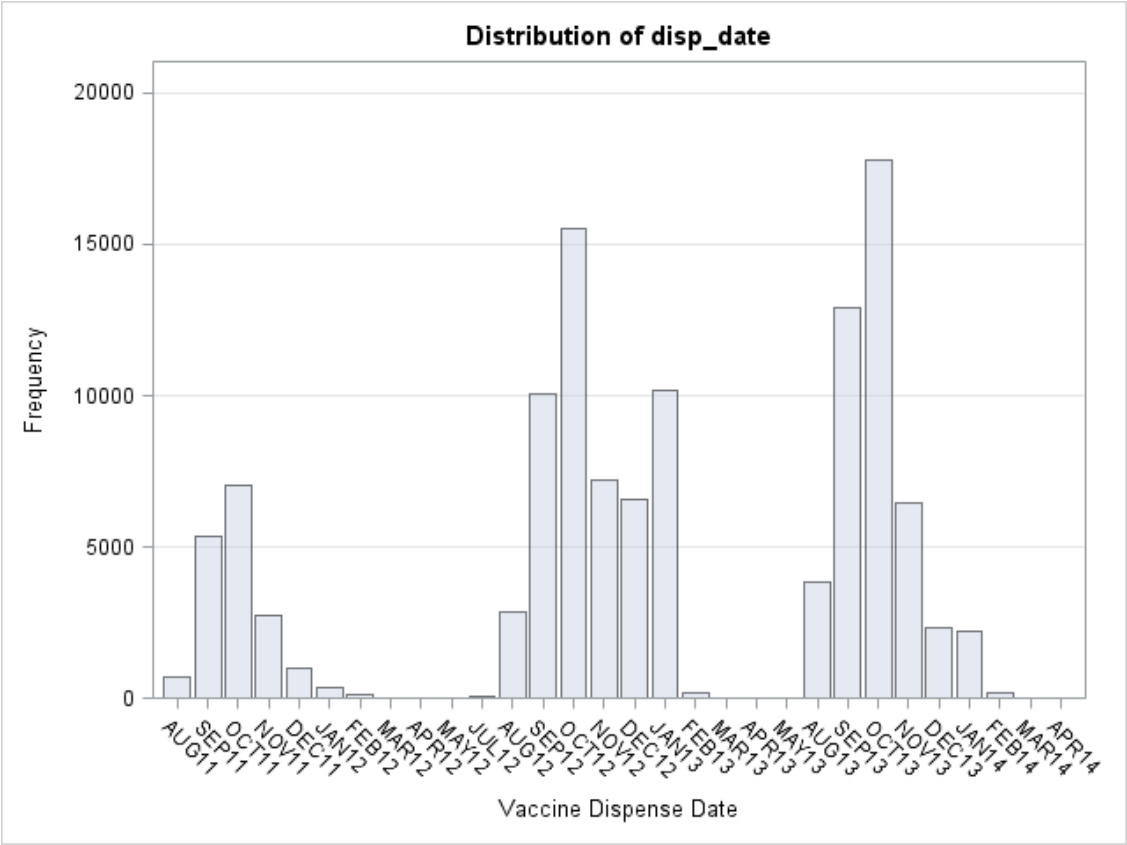

Figure 1. Monthly Distribution of Vaccine Since July 2011

Figure 1 shows a peak in vaccinations in September and October for the three influenza seasons that MITRE monitored. The 2012–2013 flu season shows a second vaccination peak in January 2013. This peak was possibly linked to media reports about the severity of the 2012–2013 flu season and the circulation of an unexpected variant of the H3N2 strain.

3.2.2 Vaccines Safety

The AE-MAP team assessed the safety of vaccines by screening patients who received an influenza vaccine for a pre-selected group of local and general AEs. Information gathered from product labeling and clinical studies was used to determine both the number and composition of vaccine to monitor in each flu season contained within the course of the retrospective study and to provide a baseline for expected outcomes and AE. This information is fully documented and available in Appendix O.

MITRE analyzed the retrospective EHR data for thirteen potential vaccine AEs that were reported frequently in the safety literature for influenza vaccines and were recommended by the FDA and other steering committee members. Table 3 lists the results. As expected, the observed incidence of AE closely tracks the overall usage. For instance, reports of malaise and fatigue increased from September–October 2013, coinciding with the peak in vaccination period. **Overall, the counts were too low to provide a statistical analysis; however, fatigue and malaise are known side effects from the flu vaccine. Larger sample sizes would be required to make definitive signal detection determinations.**

Table 3. Summary of Observed Adverse Event Rates

Adverse Events Observed—Retrospective Study across Three Flu Seasons Population (Denominator) = 125, 283		
Adverse Event	**Observation Window (Days after Vaccination)**	
	10 Days Frequency (N) Percentage (%)	**30 Days Frequency (N) Percentage (%)**
Fatigue and Malaise	19 0.015%	58 0.046%
Fever	–	–
Headaches	–	–
Guillain-Barre Syndrome	–	–
Seizures	–	–
Anaphylactic reaction	–	–
Poisoning by vaccines	–	–
Other AEs from vaccines	–	–
Infection following vaccination	–	–
Cut or hemorrhage during vaccination	–	–
Foreign object left in body during vaccination	–	–
Localized mass or lump	–	–
Swelling at vaccine site	2 0.002%	10 0.008%

With the goal of exploring how EHR reporting differs from the “gold standard” of the clinical studies drawn from vaccine labeling, MITRE compared these observed results to the labeling of the three vaccines, Afluria, Fluvirin, and Fluzone, that together constitute over 98% of total vaccinations within HIE’s EHR data. The largest reported clinical study within their respective packet inserts are reproduced below.

Table 4. Reported Adverse Event Rates for Afluria [6]

Afluria	Observation Window = 21 Days	
Adverse Event	Afluria N=10,015	Placebo N=5005
Local Adverse Reactions		
Tenderness (pain on touching)	69%	17%
Pain (without touching)	48%	11%
Redness	4%	<1%
Swelling	4%	<1%
Bruising	1%	1%
Systemic Adverse Events		
Headache	25%	23%
Malaise	29%	26%
Muscle aches	29%	26%
Nausea	21%	12%
Chills/Shivering	5%	4%
Fever	3%	2%

Table 5. Reported Adverse Event Rates for Fluvirin [7]

Fluvirin	Observation Window = 3 Days
Adverse Event	**Fluvirin N=304**
Local Adverse Reactions	
Pain	55%
Erythema	16%
Ecchymosis	7%
Induration	6%
Swelling	5%
Systemic Adverse Events	
Headache	30%
Myalgia	21%
Malaise	19%
Fatigue	18%
Sore Throat	8%
Chills	7%
Nausea	7%
Arthralgia	7%
Sweating	6%
Cough	6%
Wheezing	1%
Chest tightness	1%
Other difficulties breathing	1%
Facial edema	0%

Table 6. Reported Adverse Event Rates for Fluzone [8]

Fluzone	Observation Window = 7 Days
Adverse Event	**Fluzone N=1394**
Local Adverse Reactions	
Erythema	13.2%
Induration	10%
Swelling	8.4%
Pain	53.7%
Pruritus	9.3%
Ecchymosis	6.2%
Headache	30.3%
Myalgia	30.8%
Malaise	22.2%
Shivering	6.2%
Fever	2.6%

Multiple complicating and mitigating factors arise when aggregating or comparing these results against one another or against the Retrospective Study results. As multiple package inserts note: "Because clinical trials are conducted under widely varying conditions, adverse event rates observed in the clinical trials of a vaccine cannot be directly compared to rates in the clinical trials of another vaccine and may not reflect the rates observed in practice." [6] [8]

Some discrepancies are noted below:

1. Only the Afluria trial reports on placebo controls, making it difficult to determine the true rate of vaccine-induced AE for Fluvirin and Fluzone.
2. There is no standardized methodology for observing vaccine AE, since observation windows and reporting time-points differ from study to study.
3. There is no uniform standard for including and excluding patient self-reported symptoms. Fluzone, for instance, subdivides its AE by severity. (MITRE reported on all documented Fluzone AEs.) The other two vaccines report on any incidence, regardless of its severity. In contrast, the retrospective data in Maine's HIN is only based on EHR-input codes.
4. There is no standardized list of monitored AEs with the specific pre-screened AE varying from study to study. In addition, some AEs are catalogued differently for each vaccine (e.g., fatigue and malaise are measured jointly in some and independently in others).
5. A significant degree of variability exists in the reported frequency of AE between studies within a single vaccine. For instance, the Afluria packet insert reports on three clinical trials and lists varying side effects (e.g., tenderness ranges from 69 percent to 36 percent, redness ranges from 16 percent to 3 percent, bruising ranges from 5 percent to <1 percent). These outcomes are consistent across all package inserts and suggest that exact

incident rates are unavailable. For comparison, MITRE reported the trial from each package insert that had the highest patient sample size, ignoring multiple other studies within the insert that report differing outcomes.

The following table compares the rates of AE from the retrospective data to the three commonly dispensed vaccines in the HIN data. The table reflects the observed rates (in percentages) juxtaposed with the clinically reported rate of adverse events for the primary vaccines captured in HIN's data. MITRE only compared the list of AE we pre-set and researched during AE-MAP.

The results from the table suggest that the EHR's data capture returned a much lower frequency of AE compared to the vaccine label reports.

Table 7. Adverse Event Rates Between Retrospective Data and Reported Results

Monitored Adverse Events	**Maine HIN** N=125,283	**Afluria** N=10,015	**Fluvirin** N=304	**Fluzone** N=1394[1]
Percentage (%)	Obs.=30 days	Obs.=21 days[2]	Obs.=3 days	Obs.=7 days[3]
Fatigue and malaise	0.046	3	19[4]	22.2[5]
Fever	0	1	0	2.6
Headaches	0	2	30	30.3
Guillain-Barre Syndrome	0	0	0	0
Seizures	0	0	0	0
Anaphylactic reaction	0	0	0	0
Poisoning by vaccines	0	0	0	0
Other AEs from vaccines	0	0	0	0
Infection following vaccination	0	0	0	0
Accidental cut or hemorrhage during vaccination	0	0	0	0
Foreign object left in body during vaccination	0	0	0	0
Swelling	0.008	4	5	8.4
Localized mass or lump	0	0	6[6]	10[7]

3.2.3 Comorbidities and Concomitants Data from the Vaccine Safety Study

The MITRE analysis looked for comorbidities in the patients with vaccine AEs and noted two: swelling, and fatigue and malaise. These AEs occurred close to the vaccination date.

[1] Fluzone does not include placebo controls.
[2] Reported results are net values (subtracting placebo rates).
[3] Reported incidence categorized by severity. These numbers indicate any of the reported AEs.
[4] Malaise was reported independently of fatigue. Malaise = 19 percent, Fatigue = 18 percent
[5] Only malaise was reported.
[6] The diagnosis was induration.
[7] The diagnosis was induration.

MITRE was able to capture both comorbidity information and concomitant medication information for patients within the 10-day post-vaccination window:

- Comorbidity—From 19 patients, only 1 showed a comorbidity from the total of 19 patients with vaccine AEs. This patient had atrial fibrillation (code 427.31), which was diagnosed two weeks before the vaccination. The patient reported fatigue 24 hours after the vaccination.
- Concomitant Medication—Both patients in the AE categories of malaise and fatigue, and swelling at site of vaccination had concomitant medications in their record. The following is the list of medications with the number of patients taking them shown in parenthesis: simvastatin (6), enalapril (1), metoprolol (3), citalopram (1), fluoxetine (1), estradiol (1), prednisone (1), acetaminophen (1), acyclovir (1), atenolol (1), amitriptyline (1), ibuprofen (1), ranitidine (1), and omeprazole (1).

3.2.4 Overall Analysis of EHR Data Sufficiency for Vaccine Safety Signal Detection

MITRE first analyzed the retrospective data for vaccine AEs indicators. The analysis only used diagnostic codes to identify the AEs. Although theoretically laboratory results could be utilized for detection purposes as well, the MITRE team could not find appropriate laboratory tests that would support the vaccine's AE diagnosis list used in this study.

Over the time monitored by the retrospective study, a growing number of vaccine records were captured. This indicates that the mechanisms required to effectively monitor vaccine inoculation are increasingly in place. Although a comprehensive understanding of the precise ratio of captured records to uncaptured records is impossible to establish, sufficient volumes of vaccination data could be gathered and a safety analysis could be conducted.

This analysis, however must be caveated by a critical point. The level of severity is directly proportional to the probability of it being reported in an EHR. As the AE for vaccines typically are mild in nature they are unlikely to be significantly reported the way they would be in a highly controlled clinical study which rely on patient self-reporting. For most mild to even moderate AEs patients will often forgo reporting to a clinician. This likely accounts for a significant discrepancy between the clinical trials and the number of AEs observed. Additionally, even when symptoms were reported, if they did not result in a treatment response, were not noted in the record, or if noted, they were consigned to narrative data-fields (e.g., minor swelling at site of vaccination is unlikely to require medical intervention).

3.2.5 Vaccine Effectiveness

The AE-MAP team assessed the effectiveness of influenza vaccines based on positive influenza test results for patients with previously recorded influenza vaccinations. MITRE limited the study population to the following two populations:

- People with a vaccine dispensing record in the medications table
- People with a flu test result in the laboratory results table

Vaccine effectiveness is calculated from the population with both characteristics. This calculation was based on the generally accepted statistical method to calculate effectiveness which is detailed below.

MITRE started with people with a flu test result in the laboratory results tables provided by HIN. MITRE then queried the vaccine dispensing record contained within the HIN medications table to identify individuals vaccinated.

MITRE queried by vaccine name to identify the vaccines in the medications table. All vaccine were assessed equally. FluMist was the only live-attenuated product used. However, the total count of use was very low (56: 125,283); it was not excluded from the analysis. The other vaccines were split virus (or subunit) formulations. To identify patients with a flu test, MITRE queried more than 400 LOINC codes. MITRE did not establish which flu tests were commonly used in this population. MITRE verified that patients were tested for influenza after the vaccination. The analysis included 5,321vaccinated people from the last two flu seasons only.

The population for the 2012 and 2013 flu season was large enough to generate statistically significant results on vaccine effectiveness. The relative risk calculation demonstrated that vaccinations reduced the chance of influenza infection by 50 percent. The test was repeated to include patients with an influenza-like illness (ILI) diagnosis and a flu test confirmation; this reduced the test population to 3,337. The results were similar—a 50 percent reduction for a chance of infection in the vaccinated group. Two important factors will affect the results, if included in the analysis. First, the population distribution was roughly 33 percent outpatient, 33 percent inpatient, and 33 percent emergency room visits; effectiveness studies are typically conducted with an outpatient population only. However, if only outpatients are included, the sample sizes would be too small. The second factor is the patient's age. There was a disproportionate number of young people—especially between 0 – 8 years old—that were in the influenza-tested population, but did not show a record of vaccination. If this subgroup received a vaccination and it was not recorded, the relative risk calculation would be skewed, and the vaccine effectiveness would be lower. The analysis also showed that vaccine effectiveness was no longer significant for 2013, if only people over 50 years old were included in the study. After examining the list of comorbidities and concomitants in the population, one could speculate that some of the vaccine breakthroughs were attributed to the patient's weakened immune system.

The following table highlights the study results. Note that the percentage only reflects the results of patients who received the influenza tests and were also vaccinated. For example, in the 2012 flu season, of the 153 vaccinated and influenza-tested population, 18 tested positive, indicating a breakthrough rate of 11.76 percent. Likewise in 2013; of the 224 vaccinated and influenza-tested population, 22 tested positive, indicating a breakthrough rate of 9.82 percent.

MITRE did not calculate frequency of breakthroughs for the 2011 flu-season because of the small sample size and inferior data collection employed by HIN over that period.

Table 8. Vaccine Effectiveness for Flu Season 2012–2013

Vaccine Effectiveness			
Controlling for Flu Season 2012			
Frequency (N) Row Percentage (%)	**Pos (+)**	**Neg (-)**	**Total**
Exposed to Vaccine	18 11.76 %	135 88.24 %	153
Not Exposed to Vaccine	563 21.51 %	2054 78.49 %	2617
Total	581	2189	2770

Table 9. Vaccine Effectiveness for Flu Season 2013–2014

Vaccine Effectiveness			
Controlling for Flu Season 2013			
Frequency (N) Row Percentage (%)	**Pos (+)**	**Neg (-)**	**Total**
Exposed to Vaccine	22 9.82 %	202 90.18 %	224
Not Exposed to Vaccine	381 16.44 %	1936 83.56 %	2317
Total	403	2138	2541

3.2.5.1 Vaccine Effectiveness Compared to Vaccine Efficacy of One Vaccine Product

Clinically rigorous vaccine efficacy is considered the gold standard for determining how effective a vaccine will be at preventing breakthrough infection with influenza viruses. These assessments are typically done pre-market in the form of placebo-controlled trials. Such an assessment was not feasible from the retrospective or real-time vaccine EHR data assessment performed by MITRE. EHR data analysis does not provide options to include proper clinical controls required to interpret the impact of extenuating circumstances (e.g., patient comorbidities); nor provides options to capture results of testing of flu strains to determine if they are a match for the vaccine. Additionally, clinically rigorous vaccine efficacy studies require the inclusion of a placebo control group; that is not possible in a post-market setting.

Vaccine effectiveness studies, in-contrast, are designed to be conducted in a post-market setting. They do not typically contain placebo controls, but do test strains to conclusively determine whether in the event of infection a genuine breakthrough has occurred, or if it is the result of a strain mismatch. This form of study is more analogous to the sorts of studies a retrospective or real-time vaccine EHR data assessment can conduct, with the limitation that influenza testing does not provide enough detail to conclusively determine breakthrough infection.

Upon reviewing the three principle vaccine brands (Afluria, Fluvirin, and Fluzone) used to vaccinate our observed population, none had post-market effectiveness studies included in their package inserts, and only one (Afluria) reported a pre-market efficacy trial result.

Even though comparing results from our survey to a pre-market efficacy trial compares fundamentally different measurements, comparing the two measures is nevertheless illustrative to indicate how a measure obtained through active post-market EHR surveillance would compare to the gold standard of vaccine efficacy determination.

A vaccine efficacy measure is derived from the following formula:

Vaccine efficacy = 1 – (vaccine infection rate/placebo infection rate)

With the numerator representing the rate of breakthrough infections, and the denominator representing the overall rate of infection, with the result being an efficacy ratio [6].

Attempting to leverage this formula using EHR data from HIN, MITRE was required to modify a few elements of the formula. The principle distinction with this study is the lack of a placebo control.

For our experimental group, MITRE used the entire population in the EHR data of flu tested patients from two influenza seasons and compared vaccinated and non-vaccinated groups.

MITRE leveraged the population of unvaccinated patients who received an influenza test to represent the placebo group in the vaccine efficacy formula. See Section I.3 of Appendix I for details on the statistical methodology for vaccine analysis (test-negative design) used by MITRE. Because the population from the EHR data needed to execute the analysis is the total population with a flu test in their record, it is possible a bias may exist in the values used to calculate the formula for efficacy rate. Table 10 and 11 below show the values used and the "efficacy" rates for flu seasons 2012-2013 and 2013-2014.

Table 10. Vaccine Efficacy for Flu Season 2012–2013

Vaccine "Efficacy"				
	Total Tested For Flu	**Laboratory Confirmed Cases**	**Infection Rate (%)**	**Efficacy Rate (%)**
Vaccinated	153	18	11.8%	45%
Not Vaccinated	2,617	563	21.5%	

Table 11. Vaccine Efficacy for Flu Season 2013–2014

Vaccine "Efficacy"				
	Total Tested For Flu	**Laboratory Confirmed Cases**	**Infection Rate (%)**	**Efficacy Rate (%)**
Vaccinated	224	22	9.8%	40%
Not Vaccinated	2,317	381	16.4%	

The results suggest an overall vaccine "efficacy" rate of 45 percent in the 2012–2013 influenza season and 40 percent in the 2013–2014 season.

In contrast, Afluria reported vaccine efficacy of 60 percent against matched influenza strains and 42 percent against unmatched strains. [6] If we assume the vaccines used during the 2012–2013 flu season contained a strain mismatch, the 45 percent vaccine effectiveness results from that season could explain the discrepancy between observed results and the data from the Afluria package insert.

More difficult to reconcile, however, are MITRE's effectiveness results of 40 percent from the 2013–2014 season being much lower than the results shown from Afluria, when a significant strain mismatch was not reported, suggesting that this method indeed cannot adequately replicate an efficacy result. Therefore, given the principle limitations of an efficacy-like study conducted on real-time or retrospective EHR data, is there any utility to this approach?

There is reason to believe that there would be. While this approach cannot compute a clinically or statistically valid effectiveness or efficacy measure, this approach, by consistently and passively measuring and comparing results across years could be an effective early-indicator of a potential issue. For instance, if a notable dip in the effectiveness of the vaccine is observed one year, it is likely an indicator either of a vaccine mismatch, or of diminished efficacy for that strain. With further study and modification, MITRE believes that this could be a tool to conduct passive monitoring of signals, potentially of all approved influenza vaccines available on the market, and detect vaccine strains of potential concern warranting additional study.

3.2.5.2 Comorbidities and Concomitants Affecting Vaccine Results

The analysis queried for comorbidities in patients showing a positive flu test result after vaccination and included the following comorbidities in their records: chronic kidney disease stage III (1); acute, chronic diastolic heart failure and congestive heart failure (1); other virus infection (EBV, CMC) (1); pneumonia (1); and atrial fibrillation (1).

Eleven patients with a positive flu test showed the following concomitants in their records: Aspirin (1); Metoprolol (1); Minocycline (1); Omeprazole (1); Indomethacin (1); Citalopram (1); Sertraline (1); Promethazine (1); Acetaminophen (2); Furosemide (3); Atenolol (1); Tacrolimus (1); Prednisone (2); Levofloxacin (1); Azithromycin (1); Clonazepam (1); Simvastatin (1); and Bupropion (2).

Because the volume of patient with comorbidities and concomitants was low, MITRE did not correlate comorbidities and concomitants to vaccine effectiveness; however, MITRE was able to extract comorbidities and concomitants data from the EHRs data from HIN.

3.2.6 Overall Assessment of EHR Data Sufficiency for Vaccine Effectiveness Signal Detection

MITRE analyzed the retrospective data to conduct a limited assessment of vaccine effectiveness. Vaccine effectiveness analysis combines the vaccine dispensing data derived from the medications data table provided by HIN and, in the case of influenza vaccine effectiveness, data from laboratory test results from the influenza infection testing. Look-up tables prepared for

querying EHR data included the list of laboratory tests and proper associated LOINC designations and the names of the influenza vaccines. Laboratory tests needed to measure vaccine effectiveness and results from influenza infection were available and sufficient. However, the intersection of patients showing a vaccination in their EHR and a post-vaccination influenza test was very small. Monitoring records for instances of influenza infection can indicate a vaccine's effectiveness, particularly if it is matched or mismatched to dominant, circulating strains in a given influenza season.

3.3 Antiviral Safety

For AE-MAP, antiviral safety was monitored by following patients who were prescribed Oseltamivir (Tamiflu) for a set period following prescription. We focused on Tamiflu after finding that over 99% of the patients receiving an influenza antiviral in the HIN's data were prescribed Tamiflu. MITRE selected the AEs to monitor based on those in which signals may be identified without confounding natural influenza infection symptoms. To compare results, MITRE added AEs where natural influenza infection would confound causality (e.g., nausea and vomiting).

In addition to nausea and vomiting, the AEs monitored were:

- Acute respiratory failure requiring endotracheal intubation and ventilator therapy
- Anemia
- Seizures
- Delirium
- Cardiac arrest (heart attack and myocardial infarction)
- Life-threatening arrhythmia
- Death
- Severe congestive heart failure requiring hospitalization
- Life-threatening gastrointestinal bleeding requiring transfusion
- Renal failure requiring dialysis
- Stroke
- Coma
- Liver failure
- Severe leukopenia
- Thrombocytopenia
- The following AEs were added to the real-time exercises only:
    - Ataxia
    - Confusion
    - Encephalopathy
    - Hallucinations
    - Mental disorder

- Psychosis.

The clinical context for the antiviral safety study was gathered from product labels and clinical studies. This provided a baseline for expected AEs. Details of reported clinical studies are available in Appendix P.

In the succeeding sections, MITRE presents the results of its retrospective analysis and conducts a comparative outcomes assessment with the clinical results.

3.3.1 Results of Influenza Antiviral Adverse Events

Review of all patient records from August 2011 through June 2014 indicated that 11,001 records indicated that influenza antiviral was dispensed. The search results by medication name defined this population as follows: 1 patient using Oseltamivir (the generic name for Tamiflu), 18 patients using Relenza, 0 using Zanamivir (the generic name for Relenza), and 10,982 patients using Tamiflu. The Tamiflu total was then reduced to 10,942 after removing duplicates in the data. Duplicates refer to the dispensing of Tamiflu more than once during a single encounter. Since the population studied primarily received Tamiflu, this retrospective analysis only analyzed the frequency of AEs from this population.

The following graph shows how often Tamiflu was dispensed during the timeframe that the data was received. Tamiflu dispensing peaked significantly between November 2012 and March 2013. This peak correlates with the severe flu season in 2012–2013.

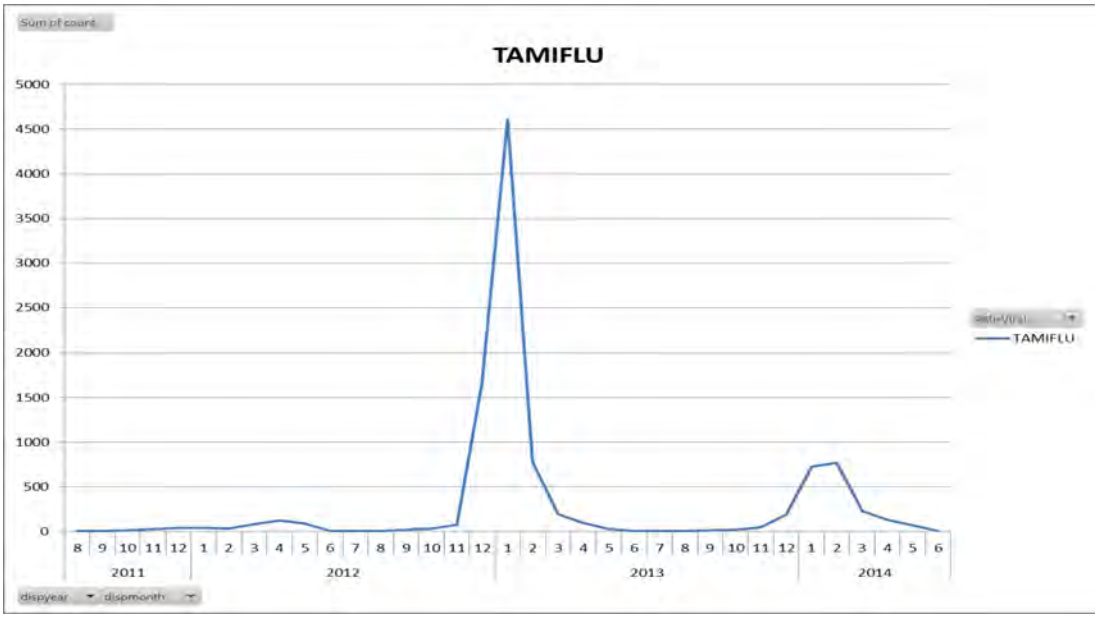

Figure 2. Tamiflu Dispensed Between August 2011 and June 2014

Algorithms were designed to follow diagnosis, procedures, and laboratory tests to infer AEs. Each AE was screened for a combination of diagnostic, procedural, and laboratory result codes that were tailored to each AE, and each code-type was given equal weight. MITRE only looked at AEs historically associated with influenza antivirals. The following table shows the sum for

each AE per patient encounter. For example, in the case of anemia, from the 10,942 Tamiflu dispensing population, MITRE found 126 instances with data elements (e.g., diagnosis, procedure, and laboratory results) in patient records that could imply an AE of interest from the encounter. MITRE searched for data elements for 30 days after Tamiflu dispensing. MITRE also searched for comorbidities (e.g., vascular, renal, hepatic, pregnancy, and obesity) 100 days before and 30 days after Tamiflu dispensing. To search for concomitant medications that could explain an observed AE (for instance, they could indicate a pre-existing condition [e.g., statins, beta-blockers], or could themselves cause the observed AE [e.g., chemotherapy drugs]), MITRE covered 30 days before and 30 days after Tamiflu dispensing.

Table 12 shows the AE count for each AE evaluated in the AE-MAP retrospective analysis. The AE percent is relative to the total Tamiflu count for the analysis period.

Table 12. Summary of AEs Initial Signals

Obs	TAMIFLU_COUNT	AE_NAME	AE_COUNT	AE_PERCENT
1	10,942	Anemia	126	1.2%
2	10,942	Arrhythmia	271	2.5%
3	10,942	Coma	0	0.00%
4	10,942	Congestive Heart Failure	12	0.11%
5	10,942	Death	1	0.01%
6	10,942	Delirium	0	0.00%
7	10,942	Gastrointestinal Bleeding	56	0.51%
8	10,942	Leukopenia	12	0.11%
9	10,942	Liver Failure	328	3.0%
10	10,942	Miscellaneous	2	0.02%
11	10,942	Myocardial Infarction	145	1.3%
12	10,942	Nausea and Vomiting	121	1.1%
13	10,942	Renal Failure	81	0.74%
14	10,942	Seizures	0	0.00%
15	10,942	Stroke	9	0.08%
16	10,942	Sudden Cardiac Arrest	1	0.01%
17	10,942	Thrombocytopenia	36	0.33%

3.3.2 Laboratory Results to Determine Signals (HL7 Codes)

The inclusion of laboratory results as data elements from the EHRs attributed significantly to the identification of initial signals. Laboratory results were considered significant, based on the code in the abnormality column in the HIN table. The abnormality column contains HL7 codes developed to flag abnormality in lab results. MITRE limited the laboratory results in its study to the following codes: HH, H, L, LL, A, AA, D, and U. Any of these codes indicated the presence of an initial signal. HIN received these codes from each laboratory that was linked to their data systems. There is no indication that coding was used uniformly across the laboratories. MITRE used the codes to assess AEs for this study. If codes were not provided, MITRE used the results value and a "man in the loop" to determine the severity of the laboratory result. Appendix Q. provides a detailed list of the HL7 result codes and their corresponding definitions.

3.3.3 Antiviral Adverse Event Signals Results

MITRE analyzed the data from all AE counts to determine if the algorithm-generated results can be used to infer each AE or if the details are generating false positives. The following sections describe the analysis results for each initial signal per AE. All results were generated from the data elements in EHR data from HIN, including inpatient and outpatient status. AEs with an asterisk should be considered for further signal refinement.

3.3.3.1 Anemia

MITRE found 126 instances of the Tamiflu-dispensed population (1.2 percent) of the total 10,492 Tamiflu-dispensed population, that had a possible signal for anemia. From this group, 46

records suggested anemia within 10 days after using Tamiflu. All 46 patients were diagnosed with anemia unspecified (code 285.9) and not with a code specifying anemia derived from drug-use. MITRE found that most patients were also diagnosed with chronic kidney disease and other renal comorbidities; therefore, this AE appeared to be the result of these comorbidities and was likely a false positive.

Laboratory data analysis identified three patients who received Tamiflu between January and February 2013. They had no diagnosis code and significantly low complete blood count (CBC) results. These patients showed no comorbidities or concomitant medications. Assuming, that a follow-on signal refinement process validates these patients as legitimate anemia sufferers and that no explanatory concomitants or comorbidities are uncovered, these patients would represent 0.03 percent of the total Tamiflu-dispensed population.

Note that the Tamiflu package inserts reporting on clinical study results indicate that less than 1 percent of patients who took Tamiflu suffered from anemia. [9]

Table 13 summarizes the observed occurrence of anemia between April 2012 and April 2014. Observed occurrences of AE spiked as Tamiflu use increased.

Table 13. Anemia AE Occurrence

Anemia				
ae_date	**Frequency**	**Percent**	**Cumulative Frequency**	**Cumulative Percent**
APR12	1	0.79	1	0.79
MAY12	3	2.38	4	3.17
DEC12	2	1.59	6	4.76
JAN13	74	58.73	80	63.49
FEB13	24	19.05	104	82.54
MAR13	1	0.79	105	83.33
OCT13	1	0.79	106	84.13
DEC13	2	1.59	108	85.71
JAN14	4	3.17	112	88.89
FEB14	6	4.76	118	93.65
MAR14	6	4.76	124	98.41
APR14	2	1.59	126	100.00

3.3.3.2 Arrhythmia*

* We marked with an asterisk those AEs we determined should be considered for further signal refinement in the future.

MITRE found 271 instances of the Tamiflu-dispensed population (2.5 percent) of the total 10,492 Tamiflu-dispensed population indicating arrhythmia; most results show the diagnosis code for atrial fibrillation (code 427.31). Two patients were diagnosed with ventricular tachycardia (code 427.1) after four and seven days of Tamiflu dispensing.

MITRE found a patient diagnosed with ventricular tachycardia during the 2012 flu season, four days after Tamiflu dispensing and with no comorbidities or concomitants. MITRE also found a patient with the same code, no comorbidities, and no concomitants in the 2013 flu season. Two patients in the 2012–2013 flu season had a high level of troponin, an atrial fibrillation diagnosis, no comorbidities, and no concomitants.

Assuming, that a follow-on signal refinement process validates these patients as legitimate arrhythmia sufferers and that no explanatory concomitants or comorbidities are uncovered, these patients would represent 0.04 percent of the total Tamiflu-dispensed population.

Note that the Tamiflu package inserts indicate that arrhythmia cases have been reported for patients taking Tamiflu; however, no quantity was specified. For clinical trials reported in the label, arrhythmia is not indicated. [9]

3.3.3.3 Coma

There were no patients with an indication of coma after Tamiflu dispensing. This aligns with Tamiflu package inserts reporting on clinical study results that do not indicate the presence of coma as a potential side-effect for patients dispensed Tamiflu for treatment. [9]

3.3.3.4 Congestive Heart Failure*

* We marked with an asterisk those AEs we determined should be considered for further signal refinement in the future

Twelve patients were diagnosed with congestive heart failure within 30 days after Tamiflu dispensing (0.11 percent). Eleven of these patients were inpatients. Eight of the 12 patients were diagnosed within 10 days after Tamiflu dispensing. Diagnosis codes found were: acute and chronic systolic heart failure (code 428.23); acute and chronic diastolic heart failure (code 428.33); acute diastolic heart failure (code 428.31); and acute on chronic combined systolic and diastolic heart failure (code 428.43). Most patients showed vascular comorbidities and no concomitants. Among the 8 patients, 1 was diagnosed with acute on chronic combined systolic and diastolic heart failure (code 428.43) within 10 days after Tamiflu dispensing and had significantly elevated troponin with no comorbidities or concomitants. This patient was seen in January 2013. Assuming that a follow-on signal refinement process validates this patient as a Tamiflu-induced congestive heart failure sufferer, it would represent an incidence rate of 0.01 percent. However, all patients received a diagnosis that only suggested congestive heart failure, not a single patient received the congestive heart failure unspecified, code 428.0 diagnosis in association with Tamiflu dispensing.

Note that the Tamiflu package inserts reporting on clinical study results do not indicate the presence of congestive heart failure as a potential side-effect for Tamiflu for treatment. [9]

3.3.3.5 Death

One patient died 30 days after taking Tamiflu, representing 0.01 percent of the total 10,492 Tamiflu-dispensed population; the cause of death was unspecified. Tamiflu package inserts reporting on clinical study results do not indicate death as a potential side-effect for patients taking Tamiflu. [9]

3.3.3.6 Delirium

There were no patients in this group. MITRE only searched for diagnosis codes for this AE. Tamiflu package inserts report on post-market incidences of delirium occurring in influenza patients receiving Tamiflu for treatment, but does not indicate a notable rate of occurrence. [9]

3.3.3.7 Gastrointestinal Bleeding*

* We marked with an asterisk those AEs we determined should be considered for further signal refinement in the future

MITRE found 56 instances of Tamiflu dispensing that suggested gastrointestinal bleeding, representing 0.51 percent of the total 10,492 Tamiflu-dispensed population. Thirty-one patients had the diagnosis code 578.1 (blood in stool). This was the only diagnosis code found. Most patients also showed high levels of creatinine in their serum, as well as vascular comorbidities. Two patients dispensed Tamiflu in January 2013 did not show a diagnosis code, but had significantly high creatinine levels within 10 days of taking Tamiflu; they showed vascular comorbidities and no concomitant medications other than omeprazole.

Note that Tamiflu package inserts reporting on voluntary post-market reporting of AE indicate that gastrointestinal bleeding cases have been reported for patients taking Tamiflu; however, there was no indication of quantity. Clinical trials reported on the label did not indicate gastrointestinal bleeding. [9]

Table 14 summarizes the observed occurrence of gastrointestinal bleeding from April 2012 to April 2014. Observed occurrences of AE spikes concurred with increased use of Tamiflu.

Table 14. Gastrointestinal AE Occurrence

Gastrointestinal Bleeding				
ae_date	**Frequency**	**Percent**	**Cumulative Frequency**	**Cumulative Percent**
DEC12	1	1.79	1	1.79
JAN13	30	53.57	31	55.36
FEB13	9	16.07	40	71.43
MAR13	2	3.57	42	75.00
APR13	1	1.79	43	76.79
DEC13	2	3.57	45	80.36
JAN14	3	5.36	48	85.71
FEB14	6	10.71	54	96.43
MAR14	2	3.57	56	100.00

3.3.3.8 Leukopenia*

* We marked with an asterisk those AEs we determined should be considered for further signal refinement in the future.

MITRE found 12 instances (0.11 percent) of Tamiflu-dispensing population that suggested possible leukopenia. No diagnosis codes were found. Six patients showed significantly low CBC results and no comorbidities. No relevant concomitant medications were found in four of the patients. One patient was taking amlodipine and another patient was taking prednisone before receiving Tamiflu; these concomitants may have contributed to the low CBC test result. Assuming that a follow-on signal refinement process validates the four remaining patients as a legitimate Tamiflu-induced leukopenia sufferers, it would represent an incidence rate of 0.04 percent.

Tamiflu package inserts do not indicate leukopenia in either pre-market trials or post-market reporting. [9]

3.3.3.9 Liver Failure*

* We marked with an asterisk those AEs we determined should be considered for further signal refinement in the future

MITRE found 328 instances (3 percent) of Tamiflu-dispensing population with data elements suggesting potential liver failure of the total 10,492 Tamiflu-dispensed population. However, MITRE did not find a diagnosis code for liver failure in the EHR data; it only found lab codes suggesting elevated liver enzymes.

MITRE found 25 patients with significantly elevated liver enzymes within 10 days after Tamiflu dispensing. Among these patients, 21 received Tamiflu in January 2013. None of the 25 patients had hepatic comorbidities, and 13 showed no comorbidities. Only two patients showed a concomitant medication, acetaminophen. Assuming that a follow-on signal refinement process validates the 11 remaining patients as a legitimate Tamiflu-induced liver failure sufferers, it would represent an incidence rate of 0.1 percent of the total Tamiflu-dispensed population.

Tamiflu package inserts indicate that there have been voluntary post-market reports of abnormal liver function test results as a consequence of Tamiflu dispensing; however, exact figures are not available. [9]

3.3.3.10 Miscellaneous*

* We marked with an asterisk those AEs we determined should be considered for further signal refinement in the future

The Miscellaneous category included patients that received either of two codes: poisoning by antiviral drugs (code 961.7) or antiviral drug causing AE (code E931.7).

MITRE found two patients who were diagnosed within 10 days after Tamiflu dispensing in January 2013; both patients had code E931.7 and neither had comorbidities or concomitants in their record. This represents 0.02 percent of the total Tamiflu-dispensed population.

3.3.3.11 Myocardial Infarction

MITRE found 145 instances of Tamiflu-dispensing population with data elements implying myocardial infarction. This represents 1.5 percent of the total 10,492 Tamiflu-dispensed population. MITRE found only one diagnosis in these records: anemia unspecified (code 285.9). Many records had high and extremely high levels of troponin. However, the frequency of

vascular comorbidities was above 60 percent, which would explain the high levels of troponin in this population. A diagnosis of anemia unspecified would not strongly correlate with myocardial infarction; therefore, this signal should be considered a false positive. Note that two patients showed extremely high troponin levels 17 and 19 days after Tamiflu dispensing. Neither patient showed comorbidities or concomitants in their record.

The Tamiflu package inserts do not indicate myocardial infarction incidences in either pre-market clinical trials or post-market voluntary reports. [9]

3.3.3.12 Nausea and Vomiting*

* We marked with an asterisk those AEs we determined should be considered for further signal refinement in the future

MITRE found 121 instances (1.1 percent) of the Tamiflu-dispensing population with relevant diagnosis codes for nausea and vomiting out of the total 10,492 Tamiflu-dispensed population. Among these patients, 71 had a relevant diagnosis code within 10 days after Tamiflu dispensing. The diagnoses and codes were vomiting alone (code 787.03); nausea with vomiting (code 787.01); and nausea alone (code 787.02). The incidence of this AE spiked between December 2012 to February 2013 and December 2013 to February 2014. No concomitant medications were found in the group. Comorbidities identified were either arrhythmia, pneumonia, or chronic kidney disease. Approximately 40 percent were emergency patients, 50 percent were outpatients, and 10 percent were inpatients.

The Tamiflu package insert showed a clinical study with placebo controls where Tamiflu was used as treatment for influenza. The frequency of nausea was 10 percent and frequency of vomiting was 9 percent (see Appendix P). Assuming that 71 patients with a relevant diagnosis code suffered symptoms of nausea and vomiting, it would represent 0.68 percent of the Tamiflu-dispensed population. Nausea and vomiting was not expected as an easily captured AE in EHR data for outpatients, since it often is underreported.

Table 15 shows the incidence of nausea and vomiting AE over time. Note that the peak in frequency coincides with the months where influenza peaks. However, since nausea and vomiting are also symptoms of influenza, the AE frequency may not be related to Tamiflu intake.

Table 15. Occurrence of Nausea and Vomiting AE

Nausea and Vomiting				
ae_date	**Frequency**	**Percent**	**Cumulative Frequency**	**Cumulative Percent**
JAN12	3	2.48	3	2.48
APR12	1	0.83	4	3.31
SEP12	1	0.83	5	4.13
DEC12	9	7.44	14	11.57
JAN13	39	32.23	53	43.80
FEB13	19	15.70	72	59.50
MAR13	6	4.96	78	64.46
APR13	1	0.83	79	65.29
SEP13	1	0.83	80	66.12
NOV13	1	0.83	81	66.94
DEC13	6	4.96	87	71.90
JAN14	13	10.74	100	82.64
FEB14	13	10.74	113	93.39
MAR14	6	4.96	119	98.35
APR14	2	1.65	121	100.00

3.3.3.13 Renal Failure*

* We marked with an asterisk those AEs we determined should be considered for further signal refinement in the future

81 individuals were identified with renal failure out of the total Tamiflu dispensing population, representing(0.47 percent). MITRE found a diagnosis code for acute kidney failure (584.9) in 51 of 53 patients in this population. Two patients had code 583.81, nephritis and nephropathy, in their record. These patients did not have a record of renal comorbidities or concomitants. The other patients in the group showed abnormal enzyme levels and no diagnosis code.

In January 2013, four patients receiving Tamiflu showed lab results with a significantly high level of serum creatinine within 10 days after dispensing. None showed renal comorbidities or concomitants. If signal refinement validates these four patients as suffering renal failure, the incidence rate would be 0.04 percent of the total Tamiflu dispensed population.

The Tamiflu package inserts do not indicate renal failure incidences in either pre-market clinical trials or post-market voluntary reports. [9]

Table 16 summarizes the observed occurrence of renal failure over the monitored interval between April 2012 and April 2014.

Table 16. Occurrence of Renal Failure AE

Renal Failure				
ae_date	**Frequency**	**Percent**	**Cumulative Frequency**	**Cumulative Percent**
SEP12	1	1.23	1	1.23
DEC12	3	3.70	4	4.94
JAN13	42	51.85	46	56.79
FEB13	14	17.28	60	74.07
MAR13	3	3.70	63	77.78
APR13	2	2.47	65	80.25
DEC13	3	3.70	68	83.95
JAN14	3	3.70	71	87.65
FEB14	7	8.64	78	96.30
MAR14	1	1.23	79	97.53
APR14	2	2.47	81	100.00

3.3.3.14 Seizures

No patients had seizures in this group. MITRE only searched for diagnosis codes for this AE.

The Tamiflu package inserts indicate that there have been voluntary post-market reports of seizures tied to Tamiflu dispensing; however, exact figures on the incidence rate were not available. [9]

3.3.3.15 Stroke*

* We marked with an asterisk those AEs we determined should be considered for further signal refinement in the future

MITRE found only nine patients in the Tamiflu-dispensed population exhibiting strokes (0.08 percent) out of the total 10,492 Tamiflu-dispensed population. The diagnosis codes were intracerebral hemorrhage (code 431) and unspecified transient cerebral ischemia (code 435.9). In January 2013, one patient showed a stroke-related diagnosis (code 435.9) within 10 days after Tamiflu dispensing. This patient showed no comorbidities or concomitant medications in the record. The Tamiflu package inserts did not indicate the incidence of strokes in either pre-market clinical trials or post-market voluntary reports. [9]

3.3.3.16 Sudden Cardiac Arrest

In February 2013, one patient in the Tamiflu-dispensed population (0.01 percent) out of the total 10,492 Tamiflu-dispensed population. The patient had a diagnosis code of cardiac arrest (code 427.5). This occurred 27 days after taking Tamiflu. No comorbidities or concomitant medications were found in the record. The Tamiflu package inserts did not report any incidence of sudden cardiac arrest in either pre-market clinical trials or post-market voluntary reports. [9]

3.3.3.17 Thrombocytopenia*

* We marked with an asterisk those AEs we determined should be considered for further signal refinement in the future.

MITRE found 36 instances of thrombocytopenia in the Tamiflu-dispensed population (0.33 percent) occurring within 30 days out of the total 10,492 Tamiflu-dispensed population. Among these instances, 24 patient records had the diagnosis for thrombocytopenia unspecified (code 287.5), and one patient had the diagnosis for other secondary thrombocytopenia (code 287.49). Thirteen of the patients were found within 10 days after Tamiflu dispensing. Three of these patients showed no diagnosis codes and significantly low CBCs. Their records did not show any comorbidities or concomitants. They were dispensed Tamiflu between January and February 2013. The Tamiflu package inserts did not report any instance of thrombocytopenia in the package inserts for either pre-market clinical trials or post-market reports.

3.3.4 Observed Data versus Anticipated Data for Antivirals

These results and observations strongly suggest we can find data elements in EHRs to find signals inferring AEs from Tamiflu dispensing. Most patients with presumed AEs were seen between January and February 2013, a time when Tamiflu dispensing peaked in the population analyzed. MITRE believes the algorithms used to query the EHRs data could be refined to avoid some noise in AEs, such as anemia and liver failure.

After initial signal refinement of the AEs marked with an asterisk, MITRE found patients with data elements indicating that the AE was associated to the time of Tamiflu dispensing. These patients' records need to undergo a signal refinement process by medical experts to establish causality. MITRE found that the diagnosis codes and laboratory results data can jointly and independently be initial signal indicators for the AEs. MITRE did not find procedure codes of interest in this population. The absence of procedures codes does not imply that they cannot be captured within EHR structured data.

As the retrospective study principally monitored for the incidence of severe AEs and antivirals are generally devoid of them, most AEs monitored in AE-MAP were not reported in the antiviral labels. Of the overlapping diagnosis, the following table showcases the discrepancies between the anticipated rate (those reported in the label) and the rates observed during AE-MAP.

Table 17. Antiviral AE Anticipated and Observed Percentages

AE_NAME	Anticipated Percentage	Observed Percentage
Nausea and Vomiting	9%	1.1%*

***1.1 percent was the rate for a 30 day window of observation. The rate was 0.68 percent for a 10 day window of observation post Tamiflu dispensing.**

Since the AEs are mild, they will not be reported as often as AEs in a highly controlled study. This will result in a significant amount of the observed discrepancy. Even if symptoms are reported, a treatment response may not be noted or, if noted, may be consigned to narrative data-fields in the EHR.

More severe AEs have a higher probability of it being reported in an EHR. As AE-MAP demonstrates with the antiviral AE results, the incidence of severe AE are effectively monitored and could trigger false-positives, due to comorbid or concomitant confounders.

This result suggests opportunities and limitations for using EHR data in near-real-time signal detection. Severe AEs corresponding to antiviral use will be detected, while less severe AE will be underreported.

3.3.5 Overall Analysis of EHR Data Sufficiency for Antiviral Safety Signal Detection

MITRE analyzed the retrospective data for antiviral AEs from the data elements available from the EHR structured data. These elements consisted of diagnostic codes and laboratory results data.

The use of laboratory results codes (LOINC) to indicate an adverse event brought the advantage of identifying an AE earlier than by use of any other codes, as well as providing an objective confirmation of the diagnosis. Using some laboratory results, however, presented their own challenges around the need to introduce criteria to pronounce an AE based on the lab result value that does not, in its own right, automatically conclude with a diagnosis. Certain labs presented binary test results (absent/present) in which the result provided a definite diagnosis. However, in many cases the result was in numeric form (a count or concentration value), that does not automatically impart a diagnosis. In these instances, numeric result values had to be assessed against the reference range, which was provided with the laboratory results data.

This reporting problem was further complicated. First, the multiple data sources providing information to HIN did not always agree on the test ranges that define “normal” laboratory results. Second, standard HL7 indicators of abnormal flags were used; this is an additional, qualitative assessment field that was included in the lab result data from HIN. The HL7 indicators such as H (above high normal) are based on the actual values reported by laboratories compared to the reference range of each test (refer to Appendix Q. for a complete list of HL7 indicators). Furthermore, laboratories providing results can override these HL7 indicators depending on criteria such as age and gender, and can add notes to the records that explain the decision to override. However, without access to these notes, the presence and justification for any of the edits is not provided. In addition, the HL7 indicators used to assess severity of a test result are not used by many of the HIN data providers analyzed, limiting the level of detail available to interpret results.

During the real-time data exercises, MITRE introduced measures for the degree of severity for laboratory results analyses. MITRE used the “Guidance for Industry Clinical Lab Values Toxicity Grading Scale” document, [4] (refer to Appendix I.

4. Near-Real-Time Signal Detection Exercises and Results

HIN sent data daily to MITRE for a real-time exercise on AEs monitoring. The real-time exercise was executed in two formats: One was receiving data daily in the ETLab at MITRE for daily data analysis and the second was running daily analysis on EHR data HIN transferred to an environment within HIN's database prepared for MITRE. This environment is referred to as the HIN sandbox. It was a virtual space where MITRE migrated the algorithms and architecture that allowed for the running of analyses to monitor for antiviral and vaccine AEs. Vaccine effectiveness was assessed both weekly and on a cumulative basis. Determination of breakthrough infection, indicating a lack of vaccine effectiveness require patients with a positive flu test result post vaccination, on a daily basis, it is not possible to accumulate enough patients in this category, therefore MITRE carried out these calculations weekly. MITRE planned to report serious adverse events using the MedWatch Form 3500A, Unexpected signal trends using a situation report, summary cumulative findings during the monitoring period in a weekly report. Because there were too few AEs to report during the exercise period, the 3-tiered reporting process was not fully implemented.

MITRE used the results from retrospective data to define baseline rates for each AE followed daily. Lookup tables were added to the query architecture to provide the baseline rates and thresholds values for the sequential analysis formula (see statistical methods section). The daily analyses calculated the sequential formula for each AE, following the same methodology described in section 5 for the querying. Each time the threshold value was reached a signal was to be indicated.

MITRE did not calculate vaccine effectiveness during the real-time data runs due to the fact that a low volume of vaccination were recorded (10 vaccinations) and none had a positive flu test result in their record. Only one patient was found with a vaccination and a flu test result and the result was negative.

4.1 Results

4.1.1 Summary of ILI Results for December 2014

MITRE leveraged the same methodology as in the retrospective analysis to analyze the frequency of ILI codes in the EHRs from the patient population from HIN and during the month of December 2014. MITRE found 3,180 patient EHRs with an ILI code. Only 315 patients from 3,180 total had a code of the P&I subset and of those 60 patient received an influenza infection diagnosis code.[8] Only one patient from the 9 dispensed a flu antiviral during the month of December had and ILI code (code 486 for Pneumonia, organism unspecified). The vast volume of ILI codes from the total of 3,180 used during December was to diagnose patients with cough, asthma, upper respiratory infection, pharyngitis, otitis media, pneumonia, sinusitis, bronchitis, fever, and chronic bronchitis in that order.

[8] The 60 patients had any of the following ICD-9 codes 487, 487.1, 487.8, 488.01, 488.02, 488.09, 488.11, 488.12, 488.19, 488.81, 488.82, and 488.89).

4.1.2 Summary of ILI Results for January 2015

MITRE used the CDC ILI codes list as in the previous month. The frequency of ILI codes usage increased. MITRE found 6,234 patient EHRs with an ILI code. Only 1,028 patients from 6,234 total had a code of the P&I subset and of those 359 patients received an influenza infection diagnosis code.[9] Only 6 patients from the 51 dispensed a flu antiviral during the month of January had an ILI code.[10] Most of the ILI codes used in January from the total of 6,234 were to diagnose cough, asthma, upper respiratory infections, pneumonia, bronchitis, pharyngitis, fever, otitis media, influenza, bronchitis, and sinusitis in that order.

Briefly, ILI codes cannot be correlated to antivirals dispensing since most patients receiving an antiviral do not have an ILI code in the structured sections of their EHR. It is possible that narrative in the record is capturing the diagnosis to dispense an antiviral unless the antiviral is being given as a preventive measure.

4.1.3 Summary of AEs from Antivirals and Vaccines Dispensing

Over the course of the real-time data monitoring exercises, covering the entire month of December 2014 and January 2015, the system only detected one signal indicating congestive heart failure (CHF) in association with Tamiflu dispensing. The signal was triggered in January 2015 by sequential analysis calculations, when a second patient was identified with a CHF diagnosis 4 days after Tamiflu dispensing. This was hospitalized case diagnosed with other conditions including acute kidney failure after several abnormal test results including glomerular filtration. The patient did not receive an ILI diagnosis and most likely was given Tamiflu as a preventive measure while treated for CHF; in addition, the patient was prescribed albuterol inhaler prior to the Tamiflu prescription. The first of the two patients diagnosed with CHF received the diagnosis two months prior to Tamiflu dispensing. Therefore, the signal was determined to be a false positive.

During the real-time monitoring exercises, 64 instances of Tamiflu dispensing were captured. No other influenza antivirals were dispensed. From that group of 64, 6 patients manifested AEs where either Tamiflu or an influenza infection may be associated to the AE. Two patients showed an anemia diagnosis, one patient was diagnosed with nausea & vomiting including elevated liver enzymes. Three additional patients showed abnormal liver enzyme laboratory results; all patients' data to indicate and AE appeared in their EHR post Tamiflu dispensing. Although the total number of patients from the real-time exercises is low, the results suggest abnormal liver enzyme levels, nausea and/or vomiting and anemia to be common AEs to find associated with influenza antivirals dispensing. Indeed, the retrospective data analysis identifies anemia, nausea & vomiting and abnormal liver enzymes possibly resulting in liver dysfunction as AEs to consider in future data analyses. Other conditions found in this group, in addition to the CHF cases discussed earlier, were one patient with atrial fibrillation and a patient with

[9] The 359 patients were diagnosed with one of the following ICD-9 codes: 487, 487.1, 487.8, 488.02, 488.81 and 488.82)

[10] ILI codes for the patients were: 490, 487.1, 491.21, 780.6, 493.9, 465.9

elevated troponin levels; in both instances their EHR data showed these as pre-existing conditions not associated with Tamiflu dispensing.

Only 10 vaccinations were captured between December 2014 and January 2015. No AEs or diagnosis codes suggesting a possible AE were identified in the EHRs of these patients.

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Appendix A. Enterprise Technology Laboratory at MITRE

MITRE's Enterprise Technology Laboratory (ETLab) provided a Federal Information Security Management Act-compliant and Health Insurance Portability and Accountability Act-compliant environment that meets the National Institute of Standards and Technology (NIST) 800-53 Moderate Baseline, where sensitive data from EHRs was hosted. Individual systems are established for each project to meet the need-to-know requirements. A dedicated system for the FDA AE-MAP maintained the project data for the study. The ETLab operates a comprehensive Security and Privacy Program that provides oversight activities, including:

- End-user training for access to the secured environment
- Guidance on transferring EHRs data from the data source to MITRE
- EHR data staging in preparation for AE-MAP staff querying and analysis
- Auditing, logging, and other NIST-mandated oversight functions
- Analysis of feasibility to obtain LDM elements from EHRs

The ETLab staff was the first line of communication with HIN to develop protocols for secure transfer of EHRs data electronically. The ETLab worked with HIN to plan and execute data staging; this process dealt with program translations (e.g., primarily from SQL to PostgreSQL) to recreate the data from HIN into "easy to follow" tables MITRE would use for data analysis. The ETLab received data from HIN daily during the near-real-time exercises. Data was staged daily for analysis. MITRE was prepared to submit reports to FDA on data results based on the protocols presented in a communications plan. In the second-half of the real-time exercise MITRE migrated the analysis algorithms developed inside the ETLab environment and into a HIN environment. This portion allowed the ETLab to serve as a data repository backup and as an alternative to continue operations in case the HIN environment failed at any time.

Appendix B. Data-Sharing Agreements

B.1 Data-Sharing Agreement Options

N.B.: The information provided here is experiential only and is not meant to constitute legal advice in any form whatsoever.

AE-MAP required a provider of EHR data able to send or transfer data to MITRE for analysis. As described below, MITRE determined that the most expedient contractual vehicle for obtaining the data necessary for AE-MAP was a Data Use Agreement (DUA). A DUA is used to describe the terms and conditions applicable to the handling/using/processing of either a Limited Data Set (as defined under the HIPAA statute) or for de-identified data (e.g., data that has been properly de-identified under the HIPAA and HITECH statutes). Appendix C. (below) details the data-fields excluded by a Limited Data Set. MITRE also determined that only structured data was useful when obtained in this manner; in other words, non-structured data would potentially bring an added hurdle onto receiving data certified as de-identified.

The DUA language defined the terms of sharing data between the parties. It included restrictions on data use and distribution, safeguards to prevent unauthorized disclosure of data and limits for the data users. The DUA terms, in essence, covered the decisions of internal meetings within the data provider in order to satisfy their limits to sharing data. Such limits will vary amongst providers. MITRE research concluded, after discussions with several potential data sources, that the terms to protect a patients' identity and health information are not covered under one single DUA template. This is because each data provider is subject to both HIPAA and to internal institutional decisions and procedures (e.g., is the data source's charter one where data is expected to be shared to improve surveillance efforts and, therefore, patient's quality of life?). This is a point to consider for future efforts to obtain EHR data because a data source may determine that their mission is not related to sharing data with third-parties monitoring AEs.

In summary, negotiations to execute a DUA are complex; if using a DUA for de-identified health information and/or for a Limited Data Set a data provider should have enough internal expertise to either achieve full de-identification of the data (e.g., a de-identified data set) or a partial de-identification of data with some personally identifiable health information remaining (e.g., a Limited Data Set) under the standards dictated by the HIPAA & HITECH statutes. A data provider should also be in a position to share data for surveillance purposes, and should be able to provide internal resources to develop queries for data extraction and transfer to the entity providing the data analysis portion (in the case of AE-MAP, MITRE).

If a data set contains protected health information (PHI) and the data set has not been redacted to be classified as a Limited Data Set, then the proper contractual vehicle for the data provider to send this data set to a data recipient will likely be a Business Associate Agreement or BAA; assuming that the data provider is a HIPAA-covered entity. Under this situation, a BAA will likely have the advantage of allowing the data recipient to work with patient's identifiable data and therefore, has the added advantage of including data providers without expertise in de-identifying patient's data. MITRE found that potential data providers tended to be accustomed to entering into a BAA only when the data recipient would provide a returned benefit from the data

analysis. This benefit primarily refers to benefits to the institution providing the data, such as an improvement in the quality of its data.

However, for present research needs, a Limited Data Set under a DUA provided MITRE with sufficient information to perform demographic surveillance, AEs initial indicators, and sequential analyses to mark signals on AEs to consider. Additionally, by restricting the DUA to a Limited Data Set, the engagement process was expedited, because there were fewer authorization requirements under HIPAA. For the purpose of AE-MAP, entering a BAA was not necessary as fully identified PHI was not needed from the data provider, just a Limited Data Set was needed. It is worth mentioning that a Limited Data Set identifies the type of data content that is excluded, not particular fields, therefore, the actual data exclusion may be applied to both structured and unstructured data. However, not all data providers have the expertise to exclude data from their systems. MITRE determined that data providers are more comfortable sharing structured data with exclusions than sharing unstructured data with exclusions. These obstacles in sharing unstructured data with exclusions may be overcome in the future through new technologies provided by EHR vendors.

MITRE learned, over the course of AE-MAP, the challenges of de-identifying unstructured data are considered too difficult to execute. As unstructured data can include any number of potential identifying details (e.g., a patient's name) within narrative, pictorial, video and other unstructured data elements, and these identifiers are essentially unpredictable, and software cannot be counted on to effectively purge all potential instances. It is MITRE's assessment that at this juncture, it is technically impossible to work with unstructured data that is also de-identified. AE-MAP was therefore limited to structured data.

Unstructured data could be of value to future endeavors in several regards. For one thing the presence of a wider array of lab result types, along with physician notes, will improve signal refinement efforts. Additionally a substantive amount of self-reported patient history data may only be contained within unstructured data.

In the future, AE-MAP can be expanded by exploring options to work virtually inside the data source. MITRE initiated such an effort with the HIE providing data for this study; however, this alternative should be explored with multiple data providers to better enhance understanding of the benefits of this approach regarding agreements and the pursuit of AE surveillance.

B.1.1 Data Partnership Agreements

N.B.: The information provided here is experiential only and is not meant to constitute legal advice in any form whatsoever.

A Limited Data Set, combined with a Data Use Agreement, was used to establish the avenue for a data provider to transmit structured data to MITRE (the research facility using the data for analysis). MITRE's observations, based on its experiences related to establishing a data partnership during this study, are captured below.

- It took 6 months to establish the DUA. However, that timeframe was longer due to initial attempts to establish a BAA. The timeframe could have been shorted by up to 3 months had a DUA been pursued initially.

  - Other agreements may precede a DUA such as internal board agreement to collaborate and data provider's agreements to participate.
  - Using the DUA template from the HIE reduced time to agreement in-place
- HIN's familiarity with the steps needed to generate Limited Data Sets facilitated the process
- MITRE found many data sources researched understand the Limited Data Set concept well while it is insufficiently practiced

Appendix C. List of EHR Elements Removed to Create a Limited Data Set

The limited data set, considered to be de-identified and shareable among research partners without an agreement in place for the sharing of PHI, contains electronic health record data with the following patient identifiers removed:

- Names
- Street addresses (other than town, city, state and zip code)
- Telephone numbers
- Fax number
- Email addresses
- Social Security
- Medical record numbers
- Health plan beneficiary numbers
- Account numbers
- Certificate license numbers
- Vehicle identifiers and serial numbers, including license plates
- Device identifiers and serial numbers
- URLs
- IP address numbers
- Biometric identifiers, including finger and voice prints
- Full face photos or comparable images.

Appendix D. Detailed Data-Partner Summary Table

Potential data partners fell into one of three categories, based on their ability to meet the partner requirements and/or their willingness to participate. The labels in no way reflect upon the quality of the data nor of the staff involved.

1. Top Tier, comprised of partners who agreed to support MITRE by providing the electronic health record (EHR) data needed for adverse event monitoring and analysis of proof of concept (AE-MAP)
2. Mid-Tier, comprised of providers who were not willing or able to contribute EHR data for this study, but who supported AE-MAP by providing insights regarding logistics and best practices and also expressed interest in participating in the future
3. Low Tier, comprised of providers who, although initially approached, did not contribute to AE-MAP.

Table 18. Prospective Data Partner Engagement Summary

Name	Description of Data Provider	Details on Potential Data Available	Electronic Health Record (EHR) System
Top Tier– Maine's HealthInfoNet (HIN)	HIN collects EHR data from providers in the state of Maine; the patient population is limited to Maine residents. HIE offers near-real-time data.	Data across provider types from providers in Maine Both inpatient and outpatient cohorts Smaller, geographically local population Access to near-real-time data	HIN includes multiple systems covering 38 hospitals and 400 practices in Maine.
Mid-Tier– US Coast Guard	The U.S. Coast Guard is a nationwide organization boasting a host of medical facilities of varying sizes; however, it is demographically limited.	Nationwide, multiple hospital and clinic system Both inpatient and outpatient cohorts Smaller demographic system Only USG agency using Epic	The U.S. Coast Guard is implementing its new Integrated Health Information System (IHiS). The IHiS, will support healthcare operations for multiple organizations, including the Coast Guard and the State Department. The IHiS is comprised of a core electronic health record system—including ambulatory, scheduling, billing and reporting features—plus other components, such as a patient portal, military history and readiness tab, military medical forms, and interface with TRICARE records.
Mid-Tier– Veterans Health Administration (VHA)	VHA is the largest, domestic provider of healthcare and boasts extensive geographic diversity. Since it exclusively services veterans, VHA is demographically limited in diversity.	Largest domestic healthcare provider-nationwide coverage Both inpatient and outpatient cohorts Large patient body that is geographically disparate but demographically homogenous	VHA uses VistA, a custom-built enterprise-wide information system built around a core EHR system. It consists of nearly 160 integrated software modules for clinical care, financial functions, and infrastructure.

Name	Description of Data Provider	Details on Potential Data Available	Electronic Health Record (EHR) System
		Possible access to near-real-time data	
Mid-Tier–Department of Defense (DoD)	The DoD operates a global network of healthcare facilities, unified under a single electronic health record system. Geographically, the DoD represents the most diverse cohort. Demographically, the cohort is limited to active-service military personnel, although this is mitigated by TRICARE beneficiaries.	Access to a global network of hospitals and clinics Both inpatient and outpatient cohorts Large patient body that is geographically disparate but demographically homogenous Possible access to near-real-time data	The DoD uses AHLTA, a custom-designed EHR system that serves as a clinical information system that generates, maintains, stores, and provides secure electronic access to comprehensive patient records.
Low Tier–UPMC	UPMC is a leading healthcare provider for Western Pennsylvania, with a consortium of hospitals and ambulatory care facilities. Their patient cohort comprises significant diversity; however, UPMC lacks geographic diversity.	Multiple hospital and clinic system in Western Pennsylvania Both inpatient and outpatient cohorts Smaller, geographically local population Possible access to near-real-time data	UPMC EHR system uses a Cerner system.
Low Tier-Athenahealth	Athenahealth, Inc. is a publicly traded American company that provides physician practices with online practice management and electronic medical record services, combined with medical billing and other healthcare business services.	Both inpatient and outpatient cohorts (primarily outpatient) Geographic and demographically large and diverse population Possible access to near-real-time data	Athena Clinicals: Integrated Electronic Medical Records service
Low Tier–Care Coordination Institute (CCI), South Carolina	CCI is a non-profit institute in South Carolina with access to 4 million patients within multiple care centers that are	Data across provider-types from providers in South Carolina Both inpatient and outpatient cohorts Smaller, geographically	CCI operations are similar to an HIE. It receives data from multiple systems and could provide access to 4 million patients in South Carolina (hospitals and practices).

Name	Description of Data Provider	Details on Potential Data Available	Electronic Health Record (EHR) System
	located primarily in South Carolina,	local population Possible access to near-real-time data	
Low Tier– Kaiser Permanente of Southern California	Kaiser Permanente of California is a large Health Maintenance Organization (HMO) that services a wide geographical area. It serves a large and diverse patient population.	Large hospital and clinic system in California Both inpatient and outpatient cohorts Larger, diverse geographically local population Possible access to near-real-time data	Kaiser Permanente uses an Epic EHR system.
Low Tier– Vanderbilt Medical University	Vanderbilt Medical Center operates a cohort of hospitals and clinics in Tennessee and Kentucky. Vanderbilt serves a large and diverse patient population, but is constrained geographically.	Multiple hospital and clinic system in Kentucky and Tennessee Both inpatient and outpatient cohorts Smaller, geographically local population Access limited to retrospective data	Vanderbilt University has a custom-developed EHR system called StarPanel.
Low Tier– Monmouth Medical Center	Monmouth Medical Center is one of New Jersey's largest, community, academic medical centers. It is affiliated with Drexel University's College of Medicine.	Single hospital Both inpatient and outpatient cohorts Smaller, geographically local population Possible access to near-real-time data.	Monmouth uses a Cerner EHR system.
Low Tier – Sibley Memorial Hospital—Johns Hopkins Medicine	Sibley is a local hospital and a member of the Johns Hopkins medical system. It serves a geographically local but demographically diverse population. Sibley has recently deployed an advanced Epic system.	Single hospital (although possible entry to a broader Johns Hopkins network.) Both inpatient and outpatient cohorts Smaller, geographically local population Access to near-real-time data Tied to Johns Hopkins University's upcoming Epic system	Sibley runs an advanced, recently installed, Epic EHR system.

Name	Description of Data Provider	Details on Potential Data Available	Electronic Health Record (EHR) System
Low Tier – Kaiser Permanente of Northern California	Kaiser Permanente of California is a large HMO servicing a geographically large area with large and diverse patient population.	Large hospital and clinic system in California Both inpatient and outpatient cohorts Larger, diverse, geographically local population Possible access to near-real-time data	Kaiser Permanente uses an Epic EHR system.

Appendix E. MITRE's Logical Data Model

MITRE's preliminary AE-MAP Logical Data Model (LDM) was developed from the Mini-Sentinel common data model. The intention was to capture a patient's history to investigate correlations of interest based on ability to capture many temporal records per patient. In coordination with the Office of Counterterrorism and Emerging Threats, the LDM was modified to capture relevant details for analyzing EHR data from patients with a presumptive diagnosis of influenza-like-illness. It integrates the structured data fields from the United States Critical Illness and Injury Trials Group Program for Emergency Preparedness (USCIITG-PREP) Data Set CRF version 2.4, Patient Data-Common Data Set combined with the Influenza Mini-Data Set. However, we did not include data elements extractable from narrative for two reasons: AE-MAP is based on structured data, and data sources were not capable of providing de-identified unstructured EHR data.

See Figure 3 for the AE-MAP LDM. The model includes eight key entities of medical relevance. The EHR data subsets required for analyses are mapped to the entities as follows:

- Patient: Describes the minimum set of de-identified information required to identify each patient. This data is necessary for analysis of records, including counting occurrences within an individual's record and across individuals. Patient data includes a patient identification (ID) and relevant demographics such as gender, age, and race.
- Vital Signs: Includes patient vitals such as blood pressure, temperature, weight, pregnancy status, and tobacco use. Vital signs define demographic elements that could be relevant for the analysis. Each patient record may contain many vital signs.
- Encounter: Includes relevant data for each encounter, such as encounter type, discharge disposition, and discharge status. Each encounter can have many possible diagnoses and procedures prescribed by a medical provider.
- Diagnoses: Includes relevant, objective medical observations for each encounter, including diagnosis codes per encounter.
- Procedures: Includes relevant medical procedures for each encounter, as identified by procedure code and procedure code type.
- Laboratory: Includes laboratory results for the patient, including when the lab was ordered, when the lab was completed, and the abnormal result indicators. Each patient record may contain laboratory data independent of the encounter.
- Dispensing: Includes the prescriptions given to the subject, and the date the drug was prescribed. Each patient record may contain many dispenses.
- Cause of Death: In the case the person dies, the causes of death will be reported, including the cause of death diagnosis code, cause of death type, source of the cause of death information, and confidence in the accuracy of the cause of death.

A data dictionary to accompany the logical data was also created. The data dictionary includes definitions for each field in the LDM as it relates to the EHR, as follows:

- Primary key: Describes relationships in the model

- Name: Describes the name of the field
- Type: Describes the type of data contained in the field (e.g., character, numeric [integer, decimal], or Boolean [True or False]).
- Not Null: Describes whether the field can be empty (e.g., “Patient ID not null = True” requires a patient ID)
- Unique: Describes whether the field is unique (i.e., if unique is true, there can be only one field per record)
- Notes: Includes the definition of the field and any amplifying information.

The graphical picture of the data model portrays the entities in boxes. The specific data fields needed for analysis is identified within the entities.

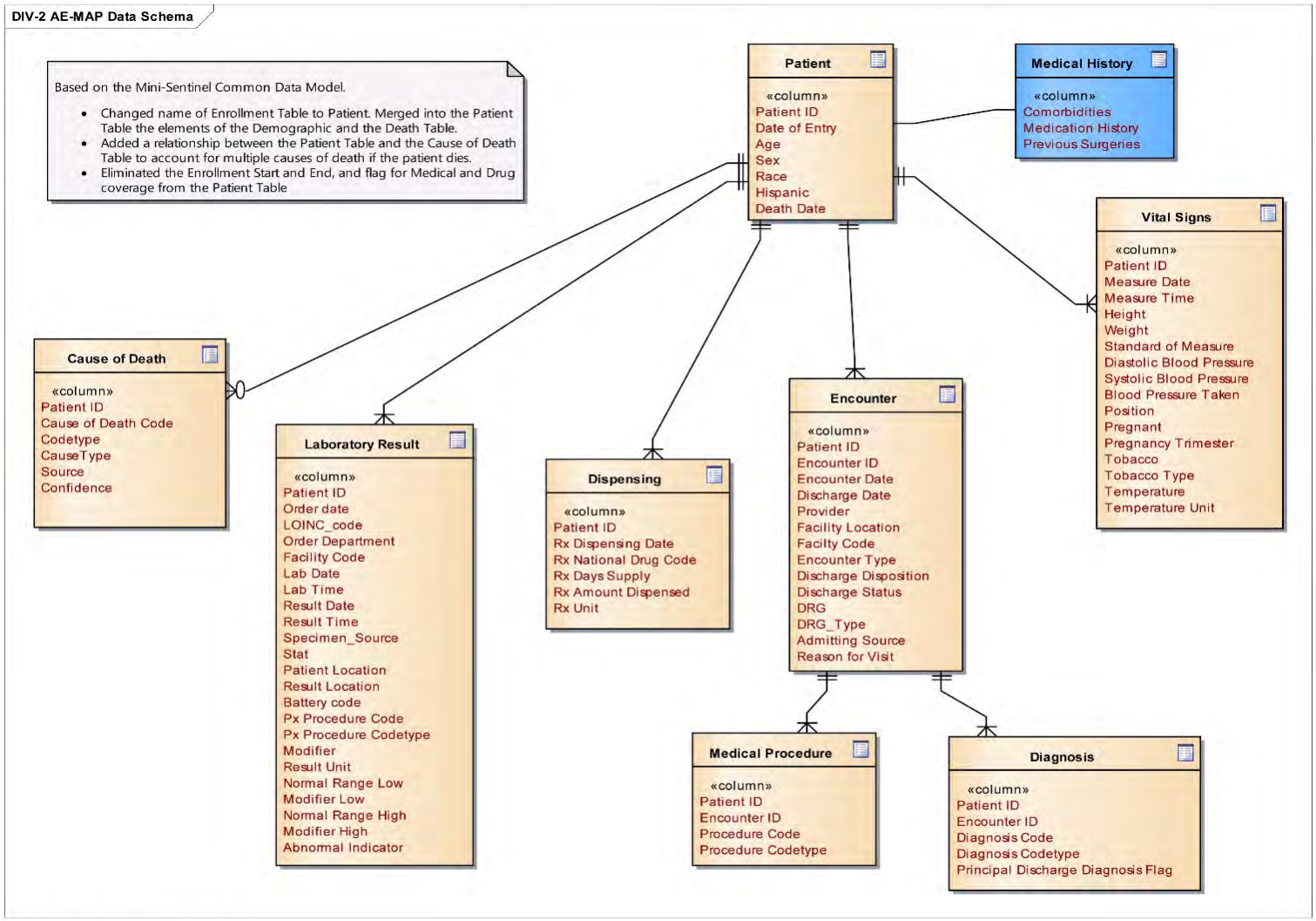


Figure 3. AE-MAP Logical Data Model Concept

Appendix F. Maine's HeathInfoNet Data

F.1 Summary of Maine's HealthInfoNet Data

Maine's HealthInfoNet (HIN) system provided MITRE with patient data for the 2011–2014 influenza seasons. Originally, MITRE requested data to be limited to patients with an influenza-like illness (ILI) diagnosis or with a record of an influenza vaccine. HIN sent all of its available electronic health record data without restriction for ILI diagnosis and from August 2011 through May 2014 for the retrospective data analysis studies. HIN sent daily data updates in December 2014 and January 2015 to cover the upcoming influenza season in near real time.

F.2 Data Fields Used in the Analysis

F.2.1 Primary Data Tables

The analysis data was primarily sourced from tables generated by HIN and based on its logical data model (LDM). Below MITRE defines the data fields for each table provided:

F.2.1.1 Medications

- **Medicationid:** A unique database table identification (ID) for every unique instance of documented medication dispensing
- **Linkid:** A unique patient identifier that spans all tables, links patients to every data point related to their care, and documents all information in the system
- **Medcode:** Unique billing code for each type of medication administered
- **Medicationname:** Text field including the name of the administered drug and the associated dosage.
- **Dispdate:** Date (dd/mm/yyyy) and time of dispensing.

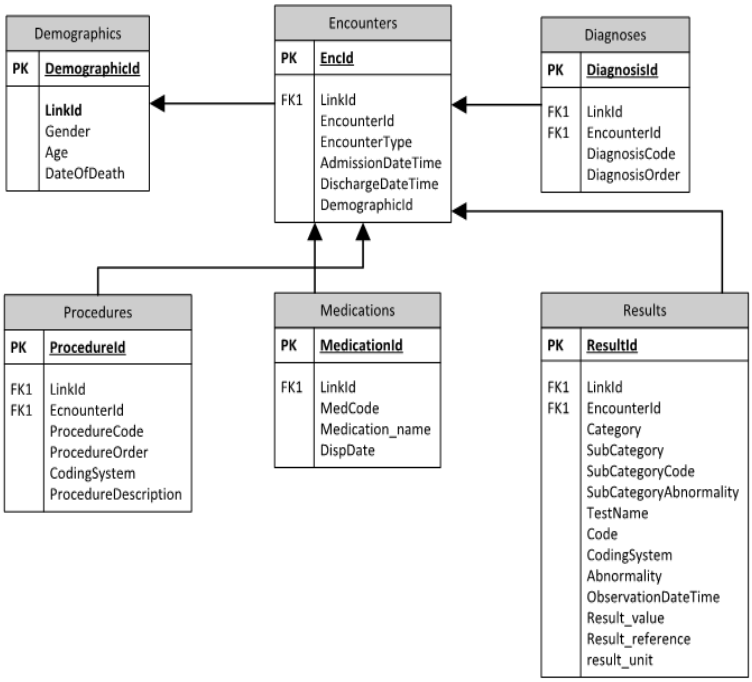


Figure 4. Maine's HIN Data Tables

The data provided by HIN includes any medications prescribed to a patient and the date of dispensing. MITRE correlated the dispensing dates to diagnosis dates to obtain diagnosis codes,

as well as diagnosis dates for comorbidities. HIN's structured data and format can inform on treatments (e.g., antibiotics dispensing) for complications with influenza, treatments associated with underlying conditions that may put someone at high risk for influenza, and treatments that may cause an AE attributed (or contributed) to influenza infection. The latter category includes chemotherapy drugs, neuropsychiatric events drugs, renal failure drugs, and non-steroidal anti-inflammatory drugs.

MITRE did not receive the regimen prescribed. For analysis purposes, MITRE assumed that the regimen was according to the product label. MITRE's did not use the National Drug Code (NDC) to follow medications, since user and provider systems lack conformity and NDC is not consistent across all systems.

F.2.1.2 Procedures

- Procedureid: A unique database table ID for every unique instance associated to a documented medication dispensing
- Linkid: A unique patient identifier that spans all tables, links patients to every data point related to their care, and documents all information in the system
- Encounterid: A unique identifier for all inpatient or ambulatory episodes of care; this identifier may render multiple procedures, laboratory tests, and diagnoses
- Procedurecode: Unique billing code for each type of procedure performed
- Procedureorder: Documentation of the sequence of multiple procedures that are performed during an encounter
- Codingsystem: Two billing code-formats used for procedure codes ICD-9 and CPT V4; field indicates which code types will appear in the corresponding "Procedurecode" column
- Proceduredescription: Text field with a description of the procedure being performed.

Procedure codes included in this study were part of the list of codes for gastrointestinal bleeding and respiratory failure AEs. These included only codes for blood transfusion, intubation, and respiratory assistance with a ventilator. MITRE did not find any patients with these codes in the data analyzed during the retrospective analysis.

F.2.1.3 Results

- Linkid: A unique patient identifier that spans all tables, links patients to every data point related to their care, and documents all information in the system
- Encounterid: A unique identifier for all inpatient or ambulatory episodes of care; this identifier may render multiple procedures, tests, and diagnoses
- Category: Meta-category code for test type (e.g., laboratory test)
- Subcategory: Text description of the type of lab test in question
- Subcategorycode: Alternate coding schema for the test being performed (not used for adverse event monitoring and analysis of proof of concept [AE-MAP])

- Subcategoryabnormality: Internally generated field that labels the result value as abnormal if it deviates from expected range (the field is still being clinically validated and was left out of the analyses presented in AE-MAP)
- Testname: Text description of the test being performed
- Code: Unique identifying code for the lab test
- Codetype: Definition of the coding type the "code" field value (e.g., logical observation identifies, names, and codes [LOINC])
- Abnormality: An HL7-formatted field that determines if the reported result is normal, abnormal, or critical (provided by the laboratory conducting the test and used to evaluate adverse events for this study)
- Observationdatetime: Date (dd/mm/yyyy) and time of lab test
- Result_value: The numeric result value of a test
- Result_reference: A normal or expected range value to evaluate the specific test (provided by the laboratories conducting the tests)
- Result_unit: The corresponding units (e.g., percentage and G/dL) for a numeric lab
- Resultid: A unique database table identification (ID) for every unique instance of documented lab result.

Flu testing information and flu test results were extracted from the results table provided by HIN. The analysis used LOINC codes to cover approximately 400 tests available in the U.S. market. A binary test result of positive/negative did not allow a measure of the accuracy of the tests. The team used the HL7 abnormality indicators A, H, and HH to identify positive test results. Analysis assumed N and Null were negative flu test results indicators in the lab results table (abnormality column) in the data provided by HIN. Laboratory test results were also used to indicate adverse events (AEs). Test results were counted when a test was included in the record at the time of dispensing. The results were then assessed with a "human in the loop" to determine if the result-value or the HL7 abnormality indicator was of a severity level enough to correlate to an AE initial signal.

F.2.1.4 Diagnoses

- Diagnosisid: A unique database table ID for every unique instance of documented diagnosis
- Linkid: A unique patient identifier that spans all tables, links patients to every data point related to their care, and documents all information in the system
- Encounterid: A unique identifier for all inpatient or ambulatory episodes of care; this identifier may render multiple procedures, tests, and diagnoses
- Diagnosiscode: Unique identifying (ICD-9) code for each diagnosis
- Diagnosisorder: Ranking of multiple diagnoses made during an encounter, based on primary, secondary, tertiary, etc. diagnosis position.

Note: Pregnancy status data is included in the diagnosis table in the LDM from HIN.

Refer to Appendix G. for an example of a table with sample data.

F.2.2 Secondary Data Tables

Secondary data tables provide supporting information that is not directly tied to the immediate analysis. These can provide additional contextual information.

F.2.2.1 Encounters

Encounters table provides additional details relating to the encounter, such as admission date and encounter type (e.g., inpatient, outpatient, emergency, and other).

F.2.2.2 Demographics

Demographics table provides additional patient details (i.e., age, gender, and date of death)

Note: Vital signs data, such as blood pressure, temperature, and weight, are not data elements captured in the LDM from HIN; therefore, they are not used in the AE-MAP.

Appendix G. Maine's HeathInfoNet Sample Data Tables

The following tables showcase the data tables and data elements provided to MITRE by Maine's HeathInfoNet. Fake sample data has been used to populate these tables for illustrative purposes.

G.1 Diagnosis Table

Diagnosis id	Link ID	Encounter RID	Diagnosis Code	Diagnosis order
1	11111	21505709	188.9	1
2	11111	21505709	535.51	1
3	11111	25328318	239.5	1
4	11111	25328318	239.5	2
5	22222	19019835	786.09	1
6	22222	19019835	786.09	2
7	22222	20605926	401.9	2
8	22222	20605926	787.01	1
9	33333	20605926	787.02	3
10	33333	21505709	883	1

G.2 Procedures Table

Procedures TableProcedure ID	linkid	encounterid	procedurecode	Procedureorder	Codingsystem	Proceduredescription
1	11111	4444444	52234	1	C4	CYSTO W/REMOVAL OF TUMORS SMALL
2	11111	4444444	89.01	2	I9	INTERVIEW AND EVALUATION, DESCRIBED AS BRIEF
3	22222	6666666	96374	3	C4	THER PROPH/DX NJX IV PUSH SINGLE/1ST SBST/DRUG
4	22222	6666666	99.29	1	I9	INJECTION OR INFUSION OF OTHER THERAPEUTIC OR PROPHYLACTIC SUBSTANCE
5	33333	7777777	99284	4	C4	EMERGENCY DEPARTMENT VISIT HIGH/URGENT SEVERITY
6	33333	7777777	12002	3	C4	SMPL REPAIR SCALP/NECK/AX/GENIT/TRUNK 2.6-7.5CM
7	33333	7777777	86.59	1	I9	CLOSURE OF SKIN AND SUBCUTANEOUS TISSUE OTHER SITES
8	33333	7777777	89.02	2	I9	INTERVIEW AND EVALUATION, DESCRIBED AS LIMITED
9	33333	7777777	99213	4	C4	OFFICE OUTPATIENT VISIT 15 MINUTES
10	33333	7777777	49587	2	C4	RPR UMBILICAL HERNIA AGE 5 YRS/> INCARCERATED

G.3 Medications Table

medicationid	linkid	medcode	medicationname	dispdate
17972677	888888	555555	HYDROCHLOROTHIAZIDE 25 MG TAB	10/9/2012 0:00
17972678	888888	555555	HYDROCHLOROTHIAZIDE 25 MG TAB	1/7/2013 0:00
17972679	888888	555555	HYDROCHLOROTHIAZIDE 25 MG TAB	4/5/2013 0:00
17972680	888888	555555	HYDROCHLOROTHIAZIDE 25 MG TAB	7/2/2013 0:00
17972681	888888	555555	HYDROCHLOROTHIAZIDE 25 MG TAB	9/30/2013 0:00
17972682	888888	555555	HYDROCHLOROTHIAZIDE 25 MG TAB	12/30/2013 0:00

G.4 Results Table

linkid	encounterid	category	subcategory	subcategorycode	subcategoryabnormality
8888888	4444444	Lab	CBC with Ordered Manual Differential panel - Blood	57782-5	Abnormal
8888888	4444444	Lab	CBC with Ordered Manual Differential panel - Blood	57782-5	Abnormal
8888888	4444444	Lab	CHEMISTRY PROFILE	CP	Normal
8888888	4444444	Lab	Basic metabolic panel - Blood	51990-0	Abnormal
8888888	4444444	Lab	CBC W Auto Differential panel - Blood	57021-8	Abnormal
8888888	4444444	Lab	CBC W Auto Differential panel - Blood	57021-8	Abnormal
8888888	4444444	Lab	Lipid panel with direct LDL - Serum or Plasma	57698-3	Abnormal
8888888	4444444	Lab	Complete blood count (hemogram) panel - Blood by Automated count	58410-2	Abnormal
8888888	4444444	Lab	Complete blood count (hemogram) panel - Blood by Automated count	58410-2	Abnormal
8888888	4444444	Lab	Follitropin [Units/volume] in Serum or Plasma	15067-2	Normal

Results Table Continued

testname	code	coding system	abnormality	observation datetime	result value	result reference	result unit	result id
Monocytes/100 leukocytes in Blood by Automated count	5905-5	LOINC	N	8/18/2018 11:18			%	836657
Neutrophils [#/volume] in Blood	26499-4	LOINC	L	8/18/2018 11:18	2.0	2.40-7.60	Thou/uL	836657
Potassium [Moles/volume] in Serum or Plasma	2823-3	LOINC	N	8/18/2018 11:18	4.0	3.6-5.0	mmol/L	836657
Bicarbonate [Moles/volume] in Plasma	1962-0	LOINC	N	8/18/2018 11:18	25	22-29	mmol/L	836657
Basophils [#/volume] in Blood by Automated count	704-7	LOINC	N	8/18/2018 11:18	0.1	0.0-0.2	K/cmm	836657
Monocytes [#/volume] in Blood by Automated count	742-7	LOINC	N	8/18/2018 11:18	0.5	0.1-0.8	K/cmm	836657
Triglyceride [Mass/volume] in Serum or Plasma	2571-8	LOINC	H	8/18/2018 11:18	155	28-149	mg/dL	836657
Hematocrit [Volume Fraction] of Blood	20570-8	LOINC	N	8/18/2018 11:18	25.0	35.0-47.0	%	836657
Hemoglobin [Mass/volume] in Blood	718-7	LOINC	N	8/18/2018 11:18	14.0	11.8-15.8	g/dL	836657
Follitropin [Units/volume] in Serum or Plasma	15067-2	LOINC	N	8/18/2018 11:18			mInt_Unit/mL	836657

Appendix H. Accessing Electronic Health Record Data

The following sections describe the different methods that MITRE explored for accessing electronic health record (EHR) data and for conducting queries to detect signals.

H.1 Different Data Storage Environments

Moving data into the Enterprise Technology Laboratory (ETLab) at MITRE was the initial approach for making the HealthInfoNet (HIN) data available for analysis. HIN sent data to MITRE's ETLab using secure file transfer protocols. This was done for both the retrospective portion of the adverse event monitoring and analysis of proof of concept (AE-MAP) and the initial real-time segment. The ETLab staff staged the data (i.e., prepared it to be readable for analysis using database utilities and transfer scripts).

For the real-time portion of AE-MAP, MITRE determined that preparing and staging data each day for analysis was extremely time-consuming for HIN and MITRE. Therefore, an environment for conducting the data analysis was created in the HIN space. This space, which was prepared by HIN and MITRE, migrated the knowledge database, data warehouse, data, and all required queries to the new space for retrospective and real-time data evaluation. MITRE worked with HIN to ensure that all applications needed for data results organization and report generation (e.g., Excel) were available to MITRE personnel. These steps were needed to expedite the data analysis in real-time.

Establishing local data environments to import, stage, and store EHR data requires an considerable expertise to handle the many technical and security concerns. In addition, the transmitting and staging data can lead to data loss and errors that may distort results.

H.2 Database Querying Methodology for Adverse Event Monitoring and Analysis of Proof of Concept

MITRE researched influenza MCM (e.g., product labels) and scientific publications to determine the adverse events (AEs) to monitor during AE-MAP. This research also identified relevant comorbidities and concomitants that affect an AE signal. All of this information was organized and developed into a knowledge database, and then was used to filter the data in queries against the HIN database (refer to Appendix F). These queries identified appropriate patients, medications, procedures, diagnoses, and lab results that met specific criteria to identify signals. They also fed information for the sequential analysis and vaccine effectiveness algorithms. Additional queries against the HIN database identified data elements for comorbidities and concomitants for patients of interest. A data warehouse was designed and created in the space to house the results from the daily analysis runs. Data was organized to allow the quick generation of summary tables with a dissection of the data elements defining an AE. MITRE database administrators designed these tables to contain patient summary data. This information could be used to identify details in the HIN database for refining a signal (e.g., medications, diagnosis, procedures, lab tests, and encounter details). Programs were written to populate the data warehouse daily. Business rules were developed to define the patient and medication selection criteria. For example, the business rules:

- Determined the length of time to look for a signal

- Determined the length of time to look for an ILI code in the record
- Determined the length of time to look for comorbidities and concomitants.

Other business rules limited data to records of relevance (e.g., an AE must occur on or after the same date as medication dispensing to be counted as part of a signal). A business rule also defined the data elements for inclusion in the results (e.g., HL7 indicator used as part of the laboratory results evaluation). (Note: The HL7 indicators populate the abnormality column in the laboratory results data tables). A business rule identified the basis of an AE (i.e., lab results, diagnosis, or procedure) that first appears on a patient's record.

Both the sequential analysis and vaccine effectiveness algorithms were implemented with queries.

Lastly, data cleansing processes were developed and implemented to remove duplicate records. This avoided the risk of counting EHRs data elements multiple times.

Overall, the knowledge database was well-populated; however, it required a significant research on the AEs and associated complications. Future studies should include enough time and proper expertise to generate details for the knowledge database. The combination of a well-crafted knowledge database and the iteratively developed queries and business rules are essential for populating the data warehouse.

Appendix I. Statistical Analysis Strategy for Adverse Event Monitoring and Analysis of Proof of Concept

AE-MAP endeavored not simply to capture and document all incidence of safety and effectiveness, but to determine when a 'signal' occurs, a trend that exceeds expectations. This requires the application of appropriate statistical methodology for signal detection.

I.1 Introduction

This section describes the statistical analyses proposed to validate the signals for each scenario on AE-MAP. Because of the smaller sample sizes, statistically significant results could not be obtained for most of the scenarios tested. However, vaccine effectiveness had sufficient data volume for using these techniques and for reporting the results. For all other scenarios, these techniques were recommended for future real-time surveillance exercises.

For AE surveillance scenarios, MITRE planned to use the maximized sequential probability ratio test (MaxSPRT) developed by Kulldorf et al. [10] [11], or similar sequential analysis methods. This section will only explain the analysis approaches using MaxSPRT. For vaccine effectiveness and other scenarios, MITRE utilized test-negative methodology or self-controlled case series methods.

I.2 MaxSPRT Method

The MaxSPRT method was built on the traditional sequential probability test (SPRT) developed by Wald [12]. In the classical SPRT, the relative risk is equal to 1 in the null hypothesis, and it is a pre-specified constant in the alternative hypothesis. With MaxSPRT, the relative risk is greater than 1, and the log likelihood ratio is maximized over all values greater than 1. For example, at a given time, let c be the observed number of an outcome (e.g., AE or ILI) and let RR denote the relative risk. Then the log likelihood ratio (LLR) test statistics is

$$LLR = \max_{r>1} ln \frac{P(c|RR = r)}{P(c|RR = 1)}$$

In an application, an alpha is pre-defined, and an upper limit for the length of surveillance is estimated from historical data or from educated simulations. A critical value is obtained from these two parameters (Kulldorf et al.). At each period (e.g., daily or weekly), the LLR is calculated. If the LLR value is greater than or equal to the critical value within the upper limit, a signal is detected. Otherwise when the upper limit is reach without the LLR crossing the critical value, the surveillance can be stopped.

MITRE used two forms of MaxSPRT. In some scenarios, the analysis used matched control groups; in other scenarios, the analysis used historical data as the reference. The first analysis compares the subject group exposed to MCM treatment with the control group. The groups are matched by sex, age group, time windows, and other factors. Critical values were estimated based on a Bernoulli distribution. The following table shows the comparison of the LLR and the critical value at the end of each period.

Table 19. Comparison of LLR and Critical-Value Based on Bernoulli Distribution

Outcome	Outcome count (subject)	Outcome count (control)	Log likelihood ratio	Critical value	Upper limit

The second form used the expected counts based on historical data. The critical values were estimated based on a Poisson distribution. The expected number of a given outcome was calculated from this historical data and input from the study population. The following table shows the comparison of the LLR and the critical value at the end of each time period.

Table 20. Comparison of LLR and Critical-Value Based on Poisson Distribution

Outcome	Outcome count (subject)	Outcome count (expected)	Log likelihood ratio	Critical value	Upper limit

Parameters and Critical Values for the Sequential Analysis

All scenarios in this study use an alpha value of 0.05 to conduct a 1-sided test.

The upper limit of the surveillance timeframe is specified by the number of the given outcome for each scenario. For the matched control analysis, it is the sum of counts in both groups and for the other analysis it is in the term of expected count. Note that upper limits are estimates based on historical data, and medical and scientific expertise. As a result, different upper limits may affect signal detection. Significant research is required for a good understanding of the upper limits. This study may use the whole influenza season—August to May—to apply the gained knowledge to later phases of the project.

Once the other parameters are calculated or determined, the critical values can be looked up from the tables generated by Kulldorf et al. [11]. Since the critical values are calculated from alpha values and the upper limits, and since the upper limits must be estimated, the signal detection will depend on the choices of the upper limits.

The antiviral scenario will be used to illustrate how to apply the approaches. The same approaches can be applied to the other scenarios.

Treatment of Influenza with an Antiviral

This analysis will identify the occurrence of AEs that may occur following the treatment of influenza with an antiviral (in the context of patient comorbidities). The target population is all patients diagnosed with influenza and using medically attended acute respiratory illness (MAARI) codes. The subject group consists of patients who are treated with a predetermined antiviral; and the control group consists of patients who are not given the antiviral.

It is assumed that the health data captured in the EHR can determine if a person has influenza and that a given AE can be determined.

Each patient was monitored for a period of 10 and 30 days, where the time interval is chosen so that a given AE can be observed within this interval. Note: the interval is 42 days for VA studies (personal communication) and for Vaccine Safety Datalink studies. [13]

Once the surveillance starts, the cumulative number of patients and the number of AEs in both groups is calculated at the end of each day or week, depending on the analysis schedule. The two groups will be matched by age, sex, and other factors.

Table 21. Sample Comparative Counts Table

	Cumulative Counts of Patients	Cumulative Counts of AE
Subject group		
Matched control group		

These numbers will be used to calculate the LLR test as in the following table.

Table 22. LLR Summary Table

Outcome	Outcome Count (Subject)	Outcome Count (Control)	Log Likelihood Ratio	Critical Value	Upper Limit
AE					

The analysis is conducted each day or week. When the LLR test exceeds the critical value, a signal is detected and the null hypothesis is rejected. Otherwise, if the upper limit is reached, the null hypothesis is not rejected.

For the two sub-scenarios, similar studies can be conducted for analyzing the effects of concurrent antibiotic use or corticosteroids and/or statins. Note that information on dispensing of antibiotic, corticosteroids, and statins can be obtained from the patient's health record. The quality of data or data availability can affect the study's results.

I.3 Test-Negative Methodology Design

Since this analysis uses observational data, it is difficult to design the comparison groups. MITRE used the test-negative design for influenza vaccine effectiveness analyses. In the test-negative design for the vaccine effectiveness scenario, people taking a test for ILI were be the population for study. Here, the EHR data determined whether individuals were vaccinated, and the laboratory test result determined a positive or negative diagnosis for ILI. With demographics considered, the data was aggregated into a table like the following and the standard definition of vaccine effectiveness (1-OR or 1-RR) was used to calculate the effectiveness and the confidence interval.

Table 23. Test-Negative Results Table

	Test Positive	Test Negative
Vaccinated		
Not Vaccinated		

I.4 Self-Controlled Case Series Methodology

Since adverse events are rare for influenza vaccines, there were few events given the population in the data. Hence instead of using MaxSPRT test, the self-controlled case series method was proposed to analyze vaccine safety. Given the predefined AEs, only people diagnosed with the

events and who were exposed to a given vaccine will be analyzed. For a given AE, a risk interval following the exposure and an equal-length interval either following the risk interval or before the exposure will be the case interval and the control interval. Statistical models, such as general linear model, were applied on the data to test the association.

I.5 Other Considerations

I.5.1 Comorbidities

For AEs, the analysis queried EHR data for certain medical conditions or comorbidities. MITRE only considered comorbidities in the following classes: renal, hepatic, respiratory, vascular, obesity, and pregnancy. MITRE used to indicate comorbidities of impact to the frequency of AEs or to vaccine effectiveness.

I.5.2 Concomitants

Concomitants medications are listed in the EHR as dispensed drugs. The presence of concomitant medications was also measured. The goal was to establish the percentage of patients taking a medication that can induce a similar AE and to list the frequency of drugs that may increase the risk of influenza or the frequency of use of drugs associated with influenza complications.

I.5.3 Influenza Vaccine Surveillance in Pregnant Women

MITRE queried for pregnancy as a comorbidity for AE, but did not find it associated with any of the observed AE in either the retrospective or real-time assessments.

I.6 Signal Refinement for the Real-Time Exercise

During the real-time data exercise for AE-MAP, MITRE introduced measures of degree of severity for laboratory results analyses. Since AE-MAP was designed to not discriminate between laboratory results, diagnosis or procedures to drive a signal to indicate an AE, it is important to refine the laboratory results based on recommended standards of results severity. MITRE used the document: “Guidance for Industry Clinical Lab Values Toxicity Grading Scale”, provided by Office of Counterterrorism and Emerging Threats (FDA) [4], to add a degree of severity when a laboratory result is driving a signal. Following this guideline document MITRE was able to classify laboratory results values as an indication of a mild, moderate, severe, or potentially life threatening situation within an AE category. For example, a blood urea nitrogen (BUN) result of over 31 mg/dL is considered a severe result and closer to be an indication of a renal failure AE while a level of 23-26 mg/dL is considered a mild indication of renal dysfunction. MITRE was able to include this degree of signal refinement where data sources provided a laboratory result value and a reference range in addition to the HL7 indicator of abnormality. MITRE determined that data sources providing data to HIN are not always providing all the data they can accommodate in their data model for laboratory results. During the retrospective data analysis it was common to find laboratory results values together with reference ranges and no HL7 indicators. It was also common to find HL7 indicators with no result value or reference range included. During the real-time exercise MITRE observed that both HL7 indicators and reference ranges were initially provided, indicating a more consistent capture of laboratory data. MITRE monitored the patients identified as candidates for AE to

assess if a result value was provided at a later time point; however, the laboratory results values were not backfilled for these patients with potential AEs.

Appendix J. Communications Process Plan

J.1 Communications Plan Purpose

To fulfill the AE-MAP expectations, the data analysis phase of the project will include an upcoming, daily, near-real-time data analysis on the EHR data collected in the field to simulate a real-world MCM surveillance scenario. As part of this surveillance project, MITRE will also simulate a comprehensive communications and reporting regimen on the ongoing and evolving results of the data analysis. A series of reports, detailed below, will help facilitate communication, provide clinical and statistical assessment on observed trends, and flag emergent signals as they are detected.

The reports generated during AE-MAP will be limited to direct government sponsors; however, the reporting process is designed to simulate communication among a wider audience, as would occur in a real-world MCM surveillance scenario.

J.2 Plan Purpose

This plan describes the processes for MITRE to communicate the AE-MAP analytics to the FDA during the data analysis phase of AE-MAP. This includes how and when MITRE will share analytics reports with FDA and the criteria for expediting reporting of AE signals of interest. The plan also serves as an operating guide for preparing reports associated with AE-MAP.

J.3 Report Formats

J.3.1 Document Properties

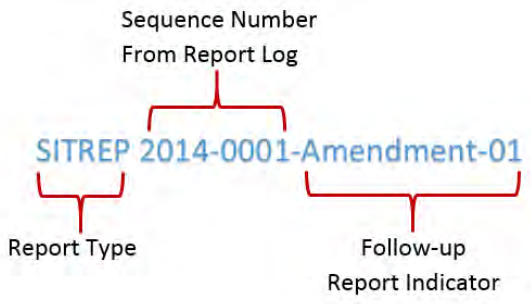
Titles are a brief, clear indication of the nature of the report.

Key words and titles are crafted to maximize utility and searchability.

Each report will include an individual's full name to complete the research.

Each report will be identified using the following sequential numbering system:

- The report type (e.g., situation report [SITREP], Form 3500A, or weekly update).
- The sequence number (i.e., calendar year and the next assigned number from the report log).
- If applicable, the word Amendment and the number of subsequent report filed on the issue to follow-on reports.



J.3.2 Reporting Format—Situation Report

A SITREP is an urgent, out-of-cycle report developed by MITRE for the FDA. It identifies significant medical trends of adverse health outcomes (e.g., renal failure, hepatic dysfunction,

adverse cardiac effects, and neurological effects) during the standard AE-MAP data analyses. Adverse health outcomes of medical significance include:

Antiviral-related AEs

Anemia (severe)

Arrhythmia

Coma

Congestive heart failure

Death

Delirium

Gastrointestinal bleeding

Leukopenia (severe)

Liver failure

Myocardial infarction

Renal failure

Respiratory failure requiring ventilation

Seizures

Stroke

Sudden cardiac arrest

Thrombocytopenia (severe)

Vaccine-related AEs

Allergic response (severe)

Anaphylaxis

Fatigue (severe)

Guillain-Barre syndrome

Headache (severe)

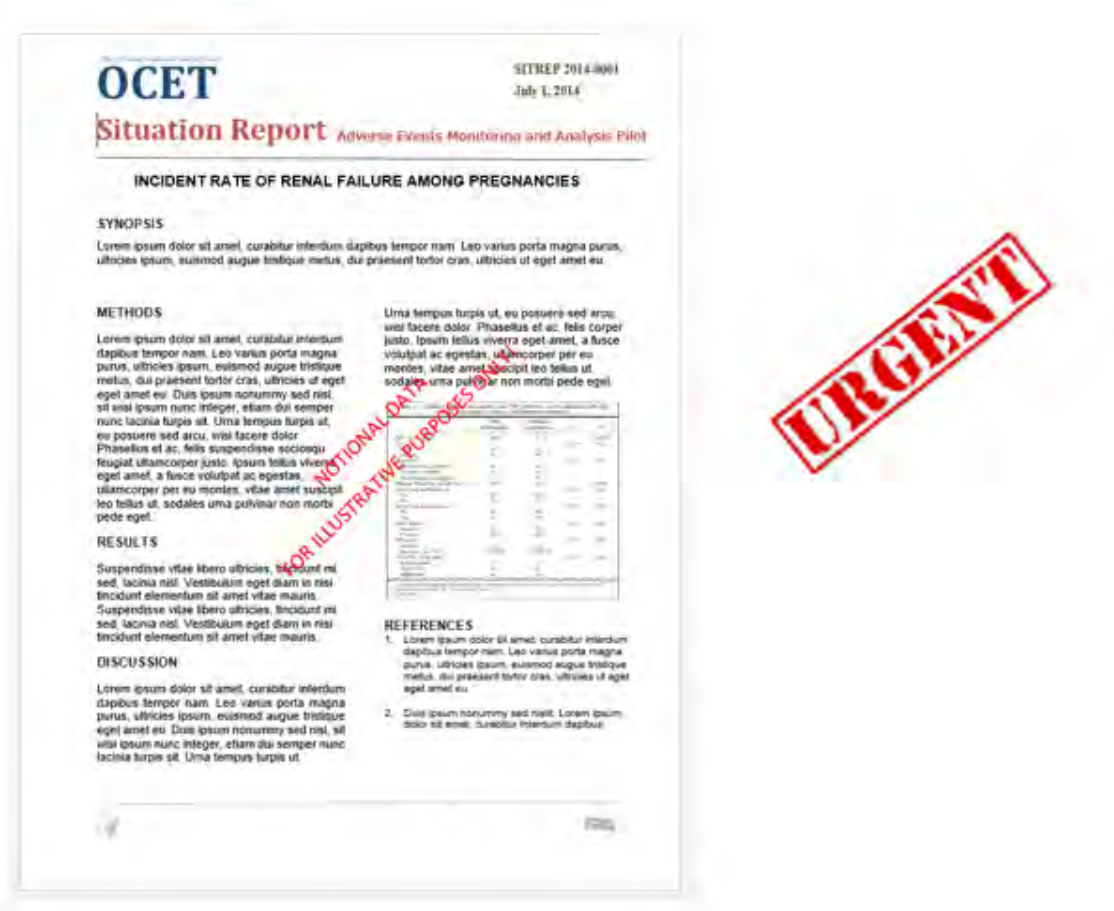
High fever

Injection site reaction (severe)

Seizure

Vaccine Effectiveness

Center for Biologics Evaluation and Research established measures of effectiveness



Every significant adverse health outcome trend identified during the AE-MAP data analyses should be captured in a SITREP. This report will be dynamic, updated by MITRE, and provided to the FDA within 24 hours. Each amended SITREP will be tracked by MITRE using the sequential numbering system described above. All one-time reports will be annotated by MITRE in the AE-MAP report log.

J.3.2.1 Situation Report Components

Synopsis

- Concisely summarizes the purpose of the report, data presented, and major conclusions in 100–200 words.

Methods

- Briefly explains the type of study
- Describes the sample and population size. Describe the patient population whose EHRs were part of the data analysis.
- Includes the Data Evaluation Design
- Describes techniques for data collection and analysis, including concomitant medications.

Results

- Concentrates on general trends and differences
- Summarizes the analysis data without discussing its implications
- Organizes data into tables, figures, graphs, etc.
  - Table data should not be duplicated in a graph or figure
- Includes titles to all figures and tables, and a legend explaining symbols, abbreviations, or special methods
- Numbers figures and tables separately and refers to them in the text by their number.

Discussion

- Interprets the data; does not restate the results
- Relates the results to existing theory and knowledge
- Speculates as necessary, but identify it as such
- Clarifies areas of doubt for further research

References and Literature Cited

- Cites only references in the paper
- Alphabetizes references by last name of the author
- Follows the recommended format for citations

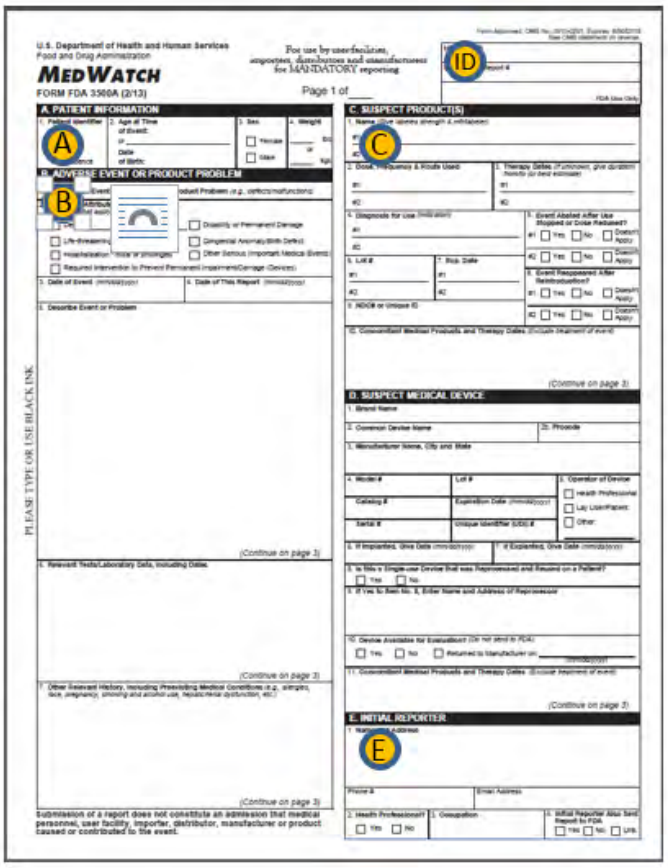
J.3.3 Reporting Format—Medwatch Form 3500A

The Medwatch 3500A form is used to report any serious unexpected adverse (SUA) event that might result from treatment of individual patients to the FDA's AE-MAP team

SUA events are described under Section B, Block 2 of the form. SUA events are:

- Death
- Life-threatening condition or illness
- Hospitalization (initial or prolongation)
- Disability or permanent damage
- Congenital anomaly or birth defect
- Other serious condition (important medical events).[11]

J.3.3.1 Protected Health Information



Report ID

All protected heath information on the 3500A will be redacted by MITRE.

Redacted 3500As will be submitted to the Office of Counterterrorism and Emerging Threats (OCET) AE-MAP project team on an ad-hoc basis within 24 hours of MITRE's awareness of an SUA event.

Assumptions

MITRE completes the 3500A using flat, structured data. The data is not intended as a substitute for the conclusions reached by a qualified physician using the full Electronic Health Record.

[11] Events related to devices were removed for this program.

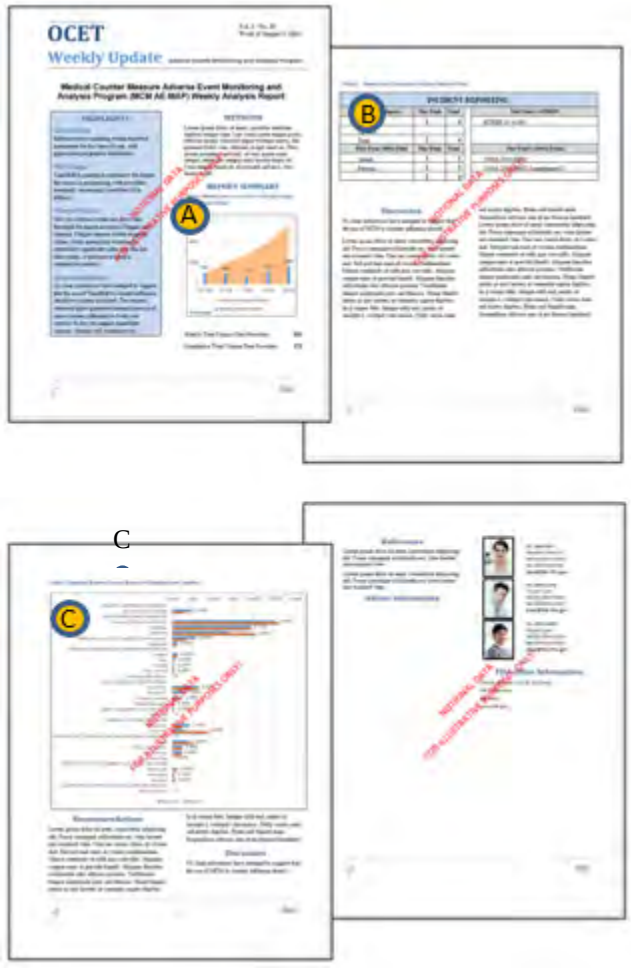
The report ID will be added to Form 3500A using the standard report convention (e.g., 2014-0003-Amendment 1). *Note: The report type is not used since the control number is being applied to the form.*

Form Population

MITRE will complete Sections A, B, C, and E of Form 3500A using the structured data available in the EHR.

J.3.4 Reporting Format—Weekly Update

The Weekly Update, developed by MITRE, provides the FDA with routine trending of expected adverse events and compares the results to those on previous reports generated as part of the surveillance program, third-party studies, and published safety documentation. The report also aggregates AEs from any Form 3500A and SITREPs processed or amended during the seven-day reporting period.



Weekly Update—Chart Summary

A. Number of cases processed during the week compared to the cumulative number of cases processed.

B. Tracking of all Form 3500A and SITReps process during the week, along with the totals submitted.

C. Comparison of known or expected levels of on-label AEs with those cases processed to date.

J.3.4.1 Weekly Update Components

Synopsis

- Concisely summarize the purpose of the report, data presented, and major conclusions 100–200 words.

Methods

- Briefly explain the type of studies run during the reporting interval.
- Sample/Population size and description. Describe the patient population whose EHRs were part of the data analysis.
- Data Evaluation Design

- Techniques for data collection and analysis, including concomitant medications

Results

- Concentrate on general trends and differences
- Summarize the data from the analysis without discussing their implications
- Organize data into tables, figures, graphs, etc.
- Organize data into previously identified AEs and newly identified (unexpected) AEs (if applicable)
- Do not duplicate table data in a graph or figure
- Title all figures and tables, and include a legend explaining symbols, abbreviations, or special methods
- Number figures and tables separately and refer to them in the text by their number

Discussion

- Interpret the data; do not restate the results
- Relate results to existing theory and knowledge
- Speculate as necessary, but identify it as such
- Clarify areas of doubt for further research

References and Literature Cited

- Cite only references in your paper and not a general bibliography on the topic
- Alphabetize by last name of the author
- Follow the recommended format for citations

J.4 Communication Distribution

All reports generated by MITRE will be communicated to OCET via email. OCET and MITRE will agree upon a predetermined set of recipients for the duration of the analysis phase for this study. Individual reports may be relayed to interested third-parties as needed and only with prior approval from OCET.

J.5 Safeguarding Information

All FDA, MITRE employees, and individuals with access to AE-MAP program materials are responsible for the securing and safeguarding sensitive program and project information. Originators of sensitive material are responsible for properly identifying and marking the material to indicate its level of sensitivity and any restrictions for disseminating the material.

J.6 Communication Log

The Communication Log, managed by MITRE, is a tracking log that registers all communications, both regular and irregular. It contains a document control number, title, author, approval authority, date of distribution, and distribution list. The register helps the AE-MAP team track all documents distributed beyond the team. Formal reports are logged using the AE-

MAP Report log. The Communication Log is not intended for distribution beyond MITRE; however, it is available on request to OCET.

J.7 Adverse Event Monitoring and Analysis of Proof of Concept Report Log

The AE-MAP Report Log is designed to inventory all reports generated as part of the analysis portion of the proof of concept. By documenting and indexing each report as it is created, the log ensures that report identifiers are never duplicated, that proper version control is maintained, and that subsequent reviews of report are easily conducted. MITRE will maintained this log internally, but will make it available to OCET upon request.

AE-MAP REPORT LOG

Control Number					Approved By	Release Date
Form 3500A SITREP / Weekly Report	Year	Sequence Number for Type of Report	Amendment (If Applicable)	Amendment Number	MITRE Project Officer	Date Released to OCET
SITREP (Example)	2013	0017	Amendment	03	J. Arroyo	30 Oct 2013
			SAMPLE			

J.8 Communications Log

The AE-MAP Communications Log will record the publication data for all formal and informal communications—analysis reports to email exchanges—generated during the analysis phase of the proof of concept. The Communications Log will capture the publication name, date author, and distribution list. It will ultimately provide a comprehensive, historical account of all communication exchanges over the course of AE-MAP and allow for easy reference and

accounting. MITRE will maintain this log internally, but will make it available to OCET upon request.

AE-MAP COMMUNICATIONS LOG

Control Number	Subject	Author	Approved By	Release Date	Distribution List
2014-001					
2014-002					
2014-003					
2014-004			SAMPLE		
2014-005					
2014-006					
2014-007					

J.9 Writing Style

This set of guidelines provides instructions and templates for writing case reports for OCET (3500 Forms, Situation and Weekly Reports). These guidelines are designed to be consistent with other research reporting.

J.9.1 Americans with Disabilities Act of 1990

Reports must comply with Section 508 accessibility standards and best practices for creating fully functional documents. Best practices, while not specifically noted in the Section 508 language, make documents useable so that technologies such as screen readers can effectively translate the information (refer to http://www.cdc.gov/training/products/AccessibleWordDocuments-html/page33971.html for best practices and help with creating 508 compliant documents).

A PDF document is the end product of most word processing documents. These software packages do most of the required work to make the document accessible. Microsoft Office 2000 and later Microsoft applications have features that assist with optimizing file accessibility.

J.9.2 Plain Writing Act of 2010

The Plain Writing Act of 2010 (http://www.gpo.gov/fdsys/pkg/PLAW-111publ274/pdf/PLAW-111publ274.pdf); requires the federal government to write all new publications, forms, and *publicly* distributed documents in a "clear, concise, well-organized" manner. Embracing this philosophy in AE-MAP reporting will promote a better understanding and acceptance of the program results.

Appendix K. Adverse Event Monitoring Landscape

Post-market surveillance (PMS) is the practice of monitoring the safety, efficacy, and performance of the Food and Drug Administration (FDA)-regulated products after the are approved for marketing. Most drugs and devices are approved on the basis of clinical trials, which involve pre-screened population subsets controlled for comorbidities and other confounding factors. PMS further refines the understanding of the safety and efficacy of medical products in real-world environments.

PMS uses a number of approaches to monitor the safety of licensed drugs, including spontaneous reporting databases, medical product event monitoring, electronic health records, patient registries and record linkage between health databases. [14]

K.1 Vaccine Adverse Events Reporting System

The National Childhood Vaccine Injury Act (NCVIA) requires healthcare providers to report adverse events (possible side effects) that occur following vaccination. In response, the FDA and Centers for Disease Control and Prevention (CDC) established the Vaccine Adverse Events Reporting System (VAERS) in 1990. VAERS is a national passive reporting system that accepts reports from the public on AEs associated with vaccines licensed in the United States. The VAERS reporting system is used to:

- Detect new, unusual, or rare vaccine AEs
- Monitor increases in known AEs
- Identify potential patient risk factors for particular types of AEs
- Identify vaccine lots with increased numbers or types of reported AEs
- Assess the safety of newly licensed vaccines

VAERS also provides a vehicle for disseminating safety-related information about the vaccine to parents and guardians, healthcare providers, vaccine manufacturers, state vaccine programs, and other constituencies. [15]

Approximately 30,000 VAERS reports are filed annually; 10–15 percent of the reports are classified as serious (i.e., resulting in permanent disability, hospitalization, life-threatening illnesses, or death). [16] The VAERS database contains reports received from 1990 to the present. Data fields in the report include: age, event category, gender, manufacturers, onset interval, recovery status, serious/non-serious category, state/territory, symptoms, vaccine, VAERS ID #, year reported, month reported, year vaccinated, and month vaccinated.

A major limitation of VAERS data is that it cannot determine if the adverse health event was caused by the vaccination or another method. [17]

K.2 Food and Drug Administration's Adverse Event Reporting System

The FDA Adverse Event Reporting System (FAERS) is an active database that contains information on all drug and therapeutic, biologic product related to AE and medication error reports submitted to the FDA. The database supports the FDA's post-marketing safety surveillance program for drug and therapeutic biologic products. AEs and medication errors are

coded to terms in the Medical Dictionary for Regulatory Activities (MedDRA) disclaimer icon terminology. The FAERS reports are evaluated by clinical reviewers in the Center for Drug Evaluation and Research and the Center for Biologics Evaluation and Research to monitor product safety after a product is approved by the FDA. If a potential safety concern is identified in FAERS, further evaluation is performed.

The FDA receives some AE and medication error reports directly from healthcare professionals (e.g., physicians, pharmacists, and nurses) and consumers (e.g., patients, family members, and lawyers). Healthcare professionals and consumers may also report AEs and/or medication errors to the products' manufacturers. If a manufacturer receives an AE report, it must send the report to the FDA, as specified by regulations. Then all reports are entered into FAERS. Reports are submitted via the Medwatch program. [18]

FAERS data have limitations. First, there is no certainty that the reported AE or medication error was due to the product, as a causal relationship between a product and event does not have to be proven. Additionally, reports do not always contain enough detail to properly evaluate an event. [19]

K.3 Sentinel Initiative

The Sentinel Initiative is a national electronic system that, when fully implemented, will enable the FDA to track the safety of drugs, biologics, and medical devices once they reach the market. [20]

Launched in May 2008 by FDA, the Mini-Sentinel was the initial pilot project sponsored by the FDA to create an active surveillance system. Mini-Sentinel used pre-existing administrative and insurance claims data from multiple sources, with collaborating institutions providing access to data, as well as scientific and organizational expertise. Most Mini-Sentinel activities focused on assessments, methods, or data assessments. [3]

Once fully deployed, the Sentinel System should enable the FDA to query diverse, automated healthcare data holders—including electronic health record systems, administrative and insurance claims databases, and registries—to evaluate possible medical product safety issues quickly and securely.

Sentinel System will be developed and implemented in stages. During its development, data will continue to be managed by its owners and questions will be sent to the data holders. Within pre-established privacy and security safeguards, these data holders will evaluate the information and send a summary of the results to the FDA. [20]

Appendix L. Steering Committee Meetings

To support the AE-MAP, a Steering Committee was formed to review the project's development and provide advice and guidance in various areas of domain expertise (e.g., scope of the AEs to monitor, patient history elements to consider, list of ILI diagnoses to follow, statistical analysis options). The Steering Committee was established in recognition of the importance of multiple third-party organizations' roles in: 1) collecting requisite data and monitoring the public health environment; 2) establishing product standards; and 3) evolving the overall Health Information Technology (HIT) market. The support, guidance, and buy-in of these third-party stakeholders is critical to the project's ultimate success. Membership in the Steering Committee was comprised of officials within the FDA and other governmental organizations. Within the FDA, participants included representatives from the Center for Biologics Evaluation and Research, the Center for Drug Evaluation and Research, the Center for Devices and Radiological Health, Office of Counterterrorism and Emerging Threats (OCET), and the Sentinel Program. Representatives from the Centers for Disease Control and Prevention and the Biomedical Advanced Research and Development Authority were also on the Steering Committee.

Throughout the proof of concept, MITRE and the Food and Drug Administration (FDA)-OCET project staff kept the Steering Committee fully informed via regular meetings and presentations pertaining to developments and findings. MITRE and the FDA-OCET also solicited advice, feedback, and comments from the Steering Committee to determine how to evolve the project to achieve the project goals.

A listing of the Steering Committee meetings, associated agendas, and deliverables follows:

- November 22, 2013: Kickoff Meeting
  - Introduced the Adverse Event Monitoring and Analysis Proof of Concept (AE-MAP) initiative. Discussed the impetus and need for AE-MAP, detailed the specific goals and overview for its approach, and provided a project elements description and timeline.
    - Deliverables: Project Overview Placemat slide deck
- January 10, 2014: Analysis Approach and Scenario Descriptions
  - Discussed how signal detection works in AE-MAP. Introduced and proposed the hybrid analytic approach (a blend of epidemiological [specific screening criteria] and discovery [open-ended data mining] methodological approaches), and introduced the antiviral and vaccine analysis scenarios for AE-MAP.
    - Deliverables: Scenario descriptions document, data analysis approach document, slide deck
- February 21, 2014: Logical Data Model and Scenario Prioritization
  - Introduced the logical data model that MITRE developed internally to map external electronic health record (EHR) data to for analysis. The analysis scenarios were reviewed again and prioritized, and ensure that appropriate questions were being asked.
    - Deliverables: Logical data model description, slide deck

- March 28, 2014: Detailed Logical Data Model Review
  - Data elements and the analysis scenarios were reviewed. Although the logical data model was briefly discussed, an additional review detailing the data elements and identifying gaps in data acquisition were needed for analysis.
    - Deliverables: Logical data model description, slide deck
- June 13, 2014: Data Analysis Methodology and Process Review
  - Recapped the scenarios for the SC. Detailed the data analysis procedure; tracking will occur from the initial signal detection through refinement and eventual AE determination. Note: This is outside of AE-MAP scope. Discussed specific goals and metrics for success.
    - Deliverables: AE-MAP Analysis Plan, slide deck
- September 5, 2014: Communications Plan and Data-Partner Update
  - Focused on two key areas: 1) update on recruiting data partners and the logistics for obtaining data, transmission, and reception. The meeting reviewed progress on the EHR data processing and the preliminary analysis and results; and 2) reviewing the planned communications processes for AE-MAP, including the process and specific report templates.
    - Deliverables: AE-MAP Communications Plan, slide deck

Appendix M. Scenarios Considered for the Proof of Concept

This section outlines the scenarios considered early and during planning the data analysis strategy for AE-MAP.

M.1 Treatment of Influenza with an Antiviral

M.1.1 Analysis to Identify Occurrence of an Adverse Events

The following scenario provides details for analyzing occurrences of the adverse events (AEs) (e.g., severe leukopenia, renal failure, stroke, and death), including in the context of comorbidities.

Description:

Conduct analyses to identify the occurrence of potential AEs subsequent to the treatment of influenza with an antiviral and within the context of patient comorbidities.

Pros:

- AEs will manifest shortly after the treatment.
- Data analysis could correlate the medical countermeasure (MCM) dose and regimen to the AEs.
- Source of the MCM is traceable.

Cons:

- AEs may be rare, and there will be very little data to analyze.

Based on the AE-MAP Logical Data Model (LDM):

- Determine which data elements within the data entities are critical for performing the analysis.
- Determine if data elements are missing within the critical data entities needed for performing the analysis.

Comorbidities and relevant medical history will be captured from data elements in the patient intake segment of the encounter section or from daily data extractions that range from 30 days prior to the MCM until post-MCM dispensing data collection.

M.1.2 Analysis of Health Outcomes for Differing Therapies

The following scenario provides details for analyzing the health outcomes of differing therapies based on the time lapse between onset and treatment.

Description:

Analyze the health outcomes of patients based on timing of the influenza-like illness (ILI) to intervention from onset of the ILI-associated symptoms.

Pros:

- AEs will manifest shortly after the treatment.
- Data analysis could correlate the drug dose and regimen to the AEs.
- Source of the drug is traceable.

Cons:

- AEs may be rare, and there will be very little data to analyze.
- Establishing when the infection occurred may be difficult.
- Monitoring the timing and consistency of dosage in an outpatient setting may be difficult.

Based on the AE-MAP LDM:

- Determine which data elements within the data entities are critical for performing the analysis.
- Determine if data elements are missing within the critical data entities needed for performing the analysis.

M.1.3 Analysis of Impact on the Health Outcomes

The following scenario provides details on analyzing the concomitant use of alterative influenza medications and how additional medication used for comorbid conditions affect the health outcomes.

Description:

Analyze the impact of treating influenza with antivirals and other potential countermeasures. Also analyze the health outcomes based on concomitant use of treatments for influenza complications (including antibiotics), treatments for underlying conditions that increase risk, and treatments that may cause AEs commonly associated with the influenza infection.

Pros:

- AEs will manifest shortly after the treatment.
- Data analysis could correlate MCM dose and regimen to the AEs.
- Source of the drug is traceable.
- A detailed dispensing record in an inpatient setting should provide a comprehensive list of the antivirals and antibiotics being administered, their dosage, and their intervals.

Cons:

- AEs may be rare, and there will be very little data to analyze.
- It is more complex to determine if AEs emerged from the MCM use or from the antibiotics use.
- It is difficult to determine a comprehensive drug regimen in an outpatient setting.

Based on the AE-MAP LDM:

- Determine which data elements within the data entities are critical for performing the analysis.

- Determine if data elements are missing within the critical data entities needed for performing the analysis.

M.2 Influenza Vaccine Surveillance

Description:

Vaccine surveillance will consist of one subset analysis that focuses on vaccine effectiveness, and a second analysis that focuses on the vaccination's AEs. Subset populations of interest, including comorbidities and pregnant women, may be extracted for comparison.

Pros:

- Access to vaccination details and definitive diagnosis may determine breakthrough cases easily.

Cons:

- An inoculation by a third party may make it difficult to determine if a vaccination has occurred.
- A record of a vaccination that occur outside of a clinical setting may only exist in free-form text (e.g., physician's notes).
- Only cases where the breakthrough infection was serious enough to go to a clinical setting can be determined.
- Only breakthrough infections that have available lab testing could be proven. (Note: Influenza-like symptoms deriving from a different strain of influenza is not a breakthrough infection.)
- Data collection requirements may need a longer window of observation.

Based on the AE-MAP LDM:

- Determine which data elements within the data entities are critical for performing the analysis.
- Determine if data elements are missing within the critical data entities needed for performing the analysis.

Pregnancy, comorbid conditions, and other relevant medical history for the study will be captured from data elements in the patient intake segment of the encounter section or from daily data extractions that range from 30 days prior to the vaccine until the post-vaccination dispensing data collection date.

Appendix N. Background on Vaccine Usage and Safety

The succeeding sections provide the necessary background and contextual information informing MITRE's retrospective analysis. Sections 6.2.1-6.2.4 provide seasonal breakdowns of vaccine products marketed domestically for each of the years in question, and notes any remarkable aspects of the season's product array. Section 6.2.5 overviews existing safety literature on influenza vaccines, drawing from both summary data and vaccine-specific package inserts.

N.1 Influenza Vaccines on the Market for the 2014–2015 Flu Season

The FDA approved the same 13 unique influenza vaccines, targeting the same influenza strains as the 2013-2014 season, manufactured by seven pharmaceutical companies for the 2014–2015 flu season. This included inactivated influenza vaccines (IIV) and live attenuated influenza vaccines (LAIV). Quadrivalent vaccine formulations (e.g., IIV4 and LAIV4) were included in this season. [21] The list of vaccines is shown below:

Table 24. Vaccines for the 2014–2015 Flu Seasons

Manufacturer	Trade Name
CSL Limited	Afluria (IIV3)
GlaxoSmithKline	Fluarix (IIV3)
	Fluarix (IIV4)
ID Biomedical Corp. of Quebec, a subsidiary of GlaxoSmithKline	FluLaval (IIV3)
	FluLaval (IIV4)
MedImmune	FluMist (LAIV4)
Novartis	Fluvirin (IIV3)
	Flucelvax (ccIIV3)
Protein Sciences Corp.	Flublok (RIV3)
Sanofi Pasteur	Fluzone (IIV3)
	Fluzone (IIV4)
	Fluzone High-Dose (IIV3)
	Fluzone Intradermal (IIV3)

N.2 Influenza Vaccines on the Market for the 2013–2014 Flu Season

The FDA approved 13 unique influenza vaccines manufactured by seven pharmaceutical companies for the 2013–2014 flu season. This included inactivated influenza vaccines (IIV) LAIV. Quadrivalent vaccine formulations (e.g., IIV4 and LAIV4) were included in this season. The list of vaccines is shown below:

Table 25. Vaccines for the 2013–2014 Flu Seasons

Manufacturer	Trade Name
CSL Limited	Afluria (IIV3)
GlaxoSmithKline	Fluarix (IIV3)
	Fluarix (IIV4)
ID Biomedical Corp. of Quebec, a subsidiary of GlaxoSmithKline	FluLaval (IIV3)
	FluLaval (IIV4)
MedImmune	FluMist (LAIV4)
Novartis	Fluvirin (IIV3)
	Flucelvax (ccIIV3)
Protein Sciences Corp.	Flublok (RIV3)
Sanofi Pasteur	Fluzone (IIV3)
	Fluzone (IIV4)
	Fluzone High-Dose (IIV3)
	Fluzone Intradermal (IIV3)

N.3 Influenza Vaccines for the 2012–2013 Flu Season

The FDA approved eight vaccines from eight manufacturers for use in the U.S. market during the 2012–2013 flu season. A quadrivalent influenza vaccine was not available for the 2012–2013 influenza season. They were: [22]

Table 26. Vaccines for the 2012–2013 Flu Seasons

Manufacturer	Trade Name
CSL Limited	AFLURIA
GlaxoSmithKline Biologicals	Fluarix
ID Biomedical Corp. of Quebec	FluLaval
MedImmune, LLC	FluMist
Novartis Vaccines and Diagnostics Incorporated	Agriflu
Novartis Vaccines and Diagnostics Limited	Fluvirin
Sanofi Pasteur, Inc.	Fluzone
Protein Sciences Corp.	Unknown

N.4 Influenza Vaccines on the Market for the 2011–2012 Flu Season

For the 2011–2012 flu season, six vaccine products were manufactured by six pharmaceutical companies. They were: [23]

Table 27. Vaccines for the 2011–2012 Flu Season

Manufacturer	Trade Name
CSL Limited	AFLURIA
GlaxoSmithKline Biologicals	Fluarix
ID Biomedical Corp. of Quebec	FluLaval
MedImmune, LLC	FluMist
Novartis Vaccines and Diagnostics Limited	Fluvirin
Sanofi Pasteur, Inc.	Fluzone

Appendix O. Vaccine Safety Profiles

The following sections detail the safety profiles of influenza vaccines reported in both summary reports from the Centers for Disease Control (CDC) and specific vaccine package inserts. Given the uniformity of vaccine safety profiles across products, summary outcomes are first reported of the overall safety of the vaccines, and then an aggregated list of the expected AE. This is then followed by specific package inserts representing both Inactivated Influenza Vaccine (IIV) and Live Attenuated Influenza Vaccine (LAIV) specific-vaccine safety information.

O.1 Overview of Vaccine Product Safety

According to the CDC all three monitored flu seasons' flu vaccines were considered safe with minimal side-effects, and have similar safety profiles as past seasonal flu vaccines. Over the years, the most common side effects of the vaccine were:

- Soreness
- Redness
- Tenderness or swelling at the site of the injection
- Nasal congestion (following the flu vaccine nasal spray) [24]

A high dose of Trivalent IIV, called **Fluzone** High-Dose, contains more antigen than the regular IIV, and it is approved for individuals who are 65 years and older. Its safety profile is similar to the regular flu vaccines. During clinical studies, the most common problems encountered after the vaccination were mild and temporary. They included pain, redness and swelling at the injection site, headache, muscle aches, fever, and malaise. Most people had minimal or no adverse effects after receiving the Fluzone High-Dose vaccine.

Another type of IIV, called Fluzone Intradermal, was approved for adults who are 18 through 64 years old. This vaccine is injected into the skin instead of the muscle. Common reactions to **Fluzone** Intradermal included redness, swelling, pain, and itching at the injection site. With the exception of pain, these side effects were more common with the intradermal vaccine than with regular flu shots. Other side effects included headache, muscle ache, and fatigue. These symptoms usually went away within three to seven days. [24]

O.2 Influenza Vaccination for Pregnant Women

According to CDC recommendations, women who are or will be pregnant during influenza season should receive IIV. LAIVs are not recommended for use during pregnancy.

Postpartum women can receive either LAIV or IIV.

Pregnant and postpartum women need not avoid contact with persons recently vaccinated with LAIV. [25]

O.3 Overview of Side Effects

The next two sections summarize the data on side effects for inactivated and live-attenuated influenza vaccines

O.3.1 Side Effects of Inactivated Influenza Vaccine

The CDC lists the following side effects to the IIV vaccination:

- Mild Reactions
  - Soreness, redness, or swelling at the location of the vaccine
  - Hoarseness, sore, red or itchy eyes, cough
  - Fever
  - Aches
  - Headache
  - Itching
  - Fatigue
- Moderate Reactions
  - Young children who get inactivated flu vaccine and pneumococcal vaccine (PCV13) at the same time may be at increased risk for seizures caused by fever.
- Severe Reactions
  - A severe allergic reaction could occur after any vaccine (estimated less than one in a million doses).
  - There is a small possibility that the inactivated flu vaccine could be associated with Guillain-Barre Syndrome (approximately one or two cases per million). [26]

The WHO compiled the following summary list of outcomes and expected incidence rate for IIV vaccines, aggregating results from multiple clinical studies. [27] The following table is reproduced from the WHO:

Table 28. IIV Vaccine Summary of Adverse Event Rates

Nature of Adverse Event	Description	Rate and Doses (According to Label) (No. of cases per 100 inoculations)
Mild	Local reactions Injection site reactions	 10–64 per 100
	Generalized reactions: Fever in children 1–5 years old	 12 per 100
	Fever in children 6–15 years old	5 per 100
Severe	Anaphylaxis	0.7 per 106
	Guillain-Barre Syndrome	1–2 per 106
	Oculo-respiratory syndrome (events of moderate severity)	76 per 106

O.3.2 Side Effects of Live Attenuated Influenza Vaccine

The CDC lists the following side effects to LAIV vaccination:

- Mild Reactions
  - Runny nose, nasal congestion, or cough
  - Fever
  - Headache and muscle aches
  - Wheezing
  - Abdominal pain or occasional vomiting or diarrhea
  - Sore throat
  - Cough, chills, fatigue/weakness
- Severe Reactions
  - A severe allergic reaction could occur after any vaccine (less than one in a million doses). [26]

The WHO compiled the following summary list of outcomes and expected incidence rate for LAIV vaccines, aggregating results from multiple clinical studies. [27] The following table is reproduced from the WHO:

Table 29. LAIV Vaccine Summary of Adverse Events Rates

Nature of Adverse event	Description	Rate and doses according to the label (No. of cases per 100 inoculations)
Mild	Local reactions:	
	Runny nose or nasal congestion	59–63 per 100
	Cough	28 per 100
	Generalized reactions:	
	Fever	16–31 per 100
	Decreased activity	16–23 per 100
	Vomiting	10 per 100
	Abdominal pain	4 per 100
	Muscle aches	14 per 100
Severe	Systemic reactions:	
	Wheezing in children of 6–11 months old	14 per 100
	Anaphylaxis	1 per 500,000

Appendix P. Background on Safety: Other Publications

P.1 Summary of Oseltamivir Safety According to Label

For the three-year observational window on retrospective data, most antiviral dispensing came in the form of Tamiflu (oseltamivir phosphate). Therefore, below we present relevant background information on Tamiflu.

Tamiflu is indicated for the treatment of uncomplicated, acute illness due to influenza infection in adults and adolescents (>13 years) who have been symptomatic for no more than two days.

Treatment is based on two Phase III clinical studies of naturally occurring influenza in adults. The predominant infection was influenza A (95 percent), a limited number of influenza B (3 percent), and an unknown influenza (2 percent)), reflecting the distribution of these strains in the community. The indication is also supported by influenza A and B challenge studies. [28]. The efficacy of Tamiflu for subjects with chronic cardiac disease and/or respiratory disease has not been established. Tamiflu is also approved for the prevention of influenza in adults and children from one year and older. The efficacy of Tamiflu for the prevention of influenza has not been established in immunocompromised patients. [29]

P.2 Tamiflu Side-Effects

Tamiflu is generally well tolerated. The most common side effects are mild to moderate nausea and vomiting, diarrhea, and stomach pain.

Treatment Studies in Adult and Adolescent Subjects (13 years of age and older): A total of 1,171 subjects who participated in adult controlled clinical trials for the treatment of influenza were treated with Tamiflu. The most frequently reported adverse events (AEs) in these studies were nausea and vomiting. These events were generally of mild to moderate severity and usually occurred on the first 2 days of administration. Less than 1 percent of subjects discontinued prematurely from clinical trials due to nausea and vomiting.

AEs that occurred with an incidence of 1 percent or greater in 1,440 subjects taking placebo or Tamiflu 75 mg twice daily in adult treatment studies are shown in Table 30. This summary includes 945 healthy young adults and 495 “at risk” subjects (elderly patients and patients with chronic cardiac or respiratory disease). Those events reported numerically more frequently in subjects taking Tamiflu compared with placebo were nausea, vomiting, bronchitis, insomnia, and vertigo.

Prophylaxis Studies in Adult and Adolescent Subjects (13 years of age and older): A total of 4,187 subjects (adolescents, healthy adults, and elderly) participated in prophylaxis studies, of whom 1,790 received the recommended dose of 75 mg once daily for up to 6 weeks. AEs were qualitatively very similar to those seen in the treatment studies, despite a longer duration of dosing (see Table 30). Events reported more frequently in subjects receiving Tamiflu compared to subjects receiving placebo in prophylaxis studies, and more commonly than in treatment studies, were aches and pains, rhinorrhea, dyspepsia and upper respiratory tract infections. However, the difference in incidence between Tamiflu and placebo for these events was less than 1 percent. There were no clinically relevant differences in the safety profile of the 942 elderly subjects who received Tamiflu or placebo, compared with the younger population. [9]

Refer to the following table for a detailed summary of the incidence of side effects in controlled clinical studies. [30]

Table 30. Summary of Tamiflu Adverse Events

	Treatment		Prophylaxis	
Adverse Event	**Tamiflu (75 mg twice daily n=724)**	**Placebo (n=716)**	**Tamiflu (75 mg once daily n=1790)**	**Placebo (n=1688)**
Nausea (w/out vomiting)	10%	6%	7%	3%
Vomiting	9%	3%	2%	1%
Diarrhea	7%	10%	3%	2%
Bronchitis	2%	2%	1%	1%
Abdominal pain	2%	2%	2%	1%
Dizziness	2%	3%	1%	1%
Headache	2%	2%	18%	18%
Cough	1%	2%	5%	7%
Insomnia	1%	1%	1%	1%
Vertigo	1%	1%	<1%	<1%
Fatigue	1%	1%	8%	10%

Appendix Q. HL7 Code List

Certain laboratory results that were monitored for the adverse events monitoring and analysis proof of concept used the HL-7 standard result codes. The following list provides the letter code and its standard definition [31]:

H	Above high normal
HH	Above upper panic limits
L	Below low normal
LL	Below lower panic limits
D	Significant change down
U	Significant change up
A	Abnormal
AA	Very abnormal

Acronyms

AE	Adverse Event
AE-MAP	Adverse Event Monitoring and Analysis of Proof of Concept
CBC	Cipher Block Chaining
CCI	Care Coordination Institute
CDC	Centers for Disease Control
DoD	Department of Defense
EHR	Electronic Health Records
ETLab	Enterprise Technology Laboratory
FDA	Food and Drug Administration
HIE	Health Information Exchange
HIN	HealthInfoNet
HIPAA	Health Insurance Portability and Accountability Act
HMO	Health Maintenance Organization
ID	Identification
IHiS	Integrated Health Information System
IIV	Inactivated Influenza Vaccines
ILI	Influenza-Like Illness
LAIV	Live Attenuated Influenza Vaccine
LDM	Logical Data Model
LLR	Log Likelihood Ratio
LOINC	Logical Observation Identifiers, Names, and Codes
MCM	Medical Countermeasure
NIST	National Institute of Standards and Technology
OCET	Office of Counterterrorism and Emerging Threats
SPRT	Sequential Probability Test
USG	United States Government
VHA	Veterans Health Administration