MINI-SENTINEL COMMON DATA MODEL EXPANSION PLAN

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

Mini-Sentinel Common Data Model Expansion Plan

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I. BACKGROUND

A. OVERVIEW OF THE MINI-SENTINEL PROGRAM

Mini-Sentinel is a pilot program sponsored by the U.S. Food and Drug Administration (FDA) as a part of its Sentinel Initiative to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products (e.g., drugs, vaccines, biologics, and medical devices). Mini-Sentinel is a major element of the Sentinel Initiative, FDA's response to Section 905 of the Food and Drug Administration Amendments Act (FDAAA) of 2007, which required FDA to create an active surveillance system using electronic health data for 100 million people by July of 2012.

During the first year of the pilot program's operation, the Mini-Sentinel Coordinating Center's (MSCC) Data Core developed a distributed data approach that utilizes the healthcare claims data of a number of collaborating Data Partners, including health insurance providers and medical centers. In addition, the Data Core developed and implemented the Mini-Sentinel Common Data Model (MSCDM) at each of the Data Partner sites. The MSCDM was designed so that, across the Data Partners, data are comparable in format and meaning, allowing the Mini-Sentinel Operations Center (MSOC) to conduct statistical analyses in a distributed manner. As of September 2012, 18 Data Partner sites had implemented the MSCDM, and the Mini-Sentinel Distributed Database network comprised the healthcare claims data of over 126 million individuals.

The MSCDM was developed to be an expandable solution to allow for inclusion of new tables containing additional types of information from other data sources. The first version of the MSCDM, developed in Year One of the Mini-Sentinel program, included information on health plan enrollment, patient demographics, medical encounters, diagnoses and procedures, outpatient pharmacy dispensings, death, and cause of death records. During Year 2, the MSCDM was expanded to include vital sign information[1] as well as the results records from 11 laboratory test types[2], all of which were chosen by the FDA's Sentinel Core team. As of September 2012, 12 of the Data Partners have incorporated lab and/or vital sign data into their CDMs. The three Mini-Sentinel Data Partners involved in the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) project have also implemented the State Vaccine Table to include immunization records held at nine immunization registries.

In Year Three of the pilot program, the MSOC is again revising the common data model to include additional clinical laboratory tests results,[3] per FDA's requests. As the Data Core's work progresses towards completion and Year Three of the Mini-Sentinel program draws to a close, the FDA is directing its attention towards future enhancements to the MSCDM.

[1] Height, weight, systolic and diastolic blood pressure, and tobacco-use status information were added in Year 2 by two Data Partners.
[2] Year 2 laboratory results included glucose, hemoglobin, hemoglobin A1c, creatinine, alanine aminotransferase, alkaline phosphatase, total bilirubin, international normalized ratio, D-dimer, lipase, absolute neutrophil count.
[3] Year 3 laboratory results included troponin-T, troponin-I, platelets, creatine kinase total, creatine kinase-MB fraction, pregnancy, influenza testing.

B. GOALS AND TASKS

To ensure that the MSCDM evolves in a way that anticipates the Agency's future needs, FDA charged the MSOC with developing a plan for expansion of the MSCDM. The MSOC was asked to consider the active surveillance needs of FDA and available data resources both within and outside the current Mini-Sentinel Data Partners and other Mini-Sentinel collaborating institutions. Specific tasks included:

- Create a workgroup to lead the process.
- Identify potential priorities for expansion. Examples might include inpatient EHR data, other clinical data priorities for FDA (blood transfusion, radiology reports, and pathology reports), and data not available within current collaborating institutions (e.g., National Death Index, registries).
- Identify gaps in the current MSCDM.
- Recommend priorities for expansion and, after the report is finalized, produce a workplan for the remainder of the pilot, addressing any gaps that may need to be filled.

II. APPROACH

The MSCDM Expansion Workgroup, led by the Data Core co-Leads, included the MSOC Data Core, Darren Toh, David Cole (MSOC), Meghan Baker (MSOC), Patrick Archdeacon (FDA-CDER), and Michael Nguyen (FDA-CBER). The workgroup met as needed during regularly scheduled Data Core calls from January 2012 through April 2012.

The workgroup solicited specific priorities for exposures of interest and health outcomes of interest (HOI) from CDER, CDRH, and CBER, and gathered information about the exposure setting, timing of outcomes with respect to exposures of interest, and capture in the current MSCDM. Specific priorities emerging from the Post-Licensure Rapid Immunization Safety Monitoring (PRISM) and Blood Safety Continuous Active-Surveillance Network (BloodSCAN) Task Orders and from the 4.10 workgroup (Routine Surveillance of Newly Approved Products) were also identified. The workgroup gathered information about additional clinical and laboratory data needed for ascertainment of HOIs from FDA and the Protocol Core. The exposures and health outcomes of interest and their related characteristics were used to guide discussion and should not be interpreted as a list of surveillance targets for FDA or an indication of future surveillance activities.

Next, the workgroup engaged the Mini-Sentinel Data Partners in structured discussions about (1) the capture of various exposures in their respective databases, (2) how the CDM might be expanded to enhance the capture of future data elements, (3) completeness of inpatient administrations of exposures of interest, and (4) completeness of medical utilization data for members with multiple sources of coverage.

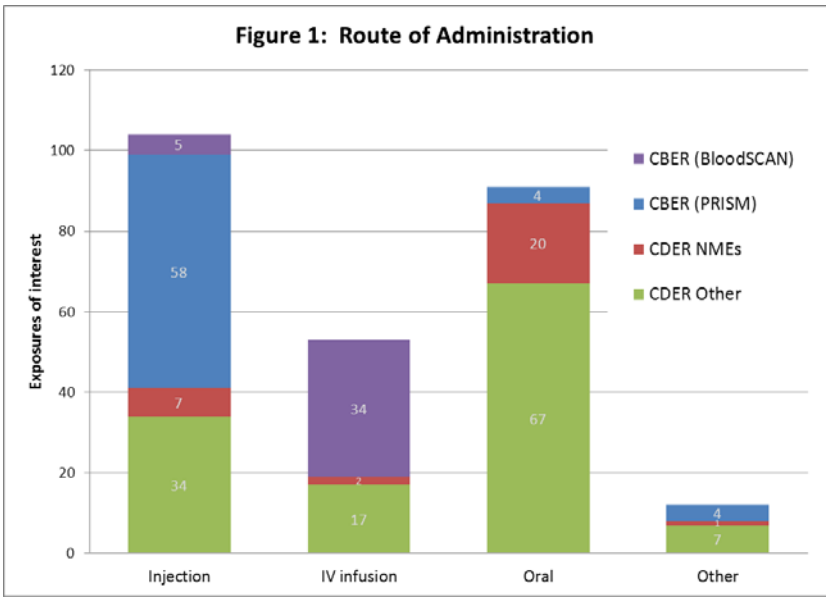
In parallel, the workgroup solicited suggestions for refinements and enhancements to the CDM from the MSOC Data Core and the other MS workgroups.

III. FINDINGS

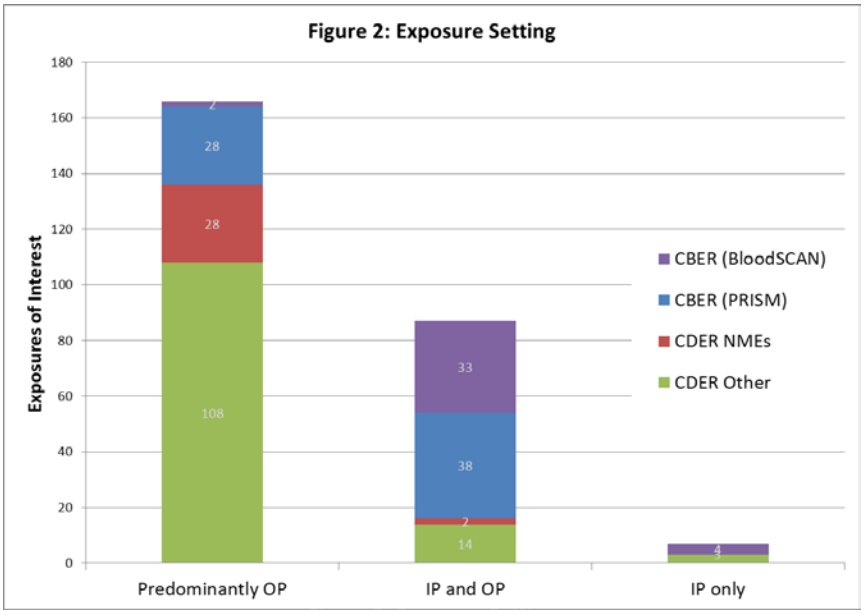
A. PRIORITY EXPOSURES AND HEALTH OUTCOMES OF INTEREST

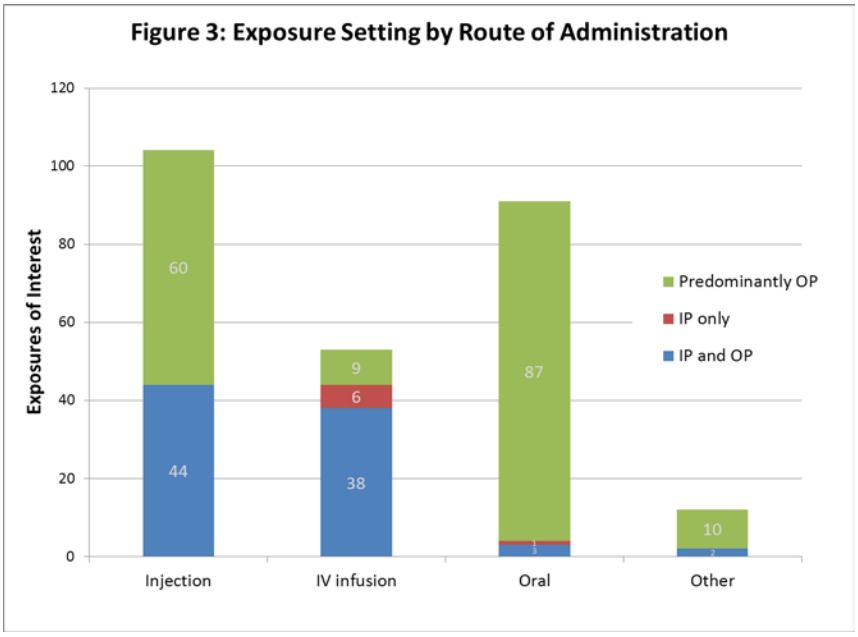
1. Exposures of Interest

In total, 260 exposures of interest were identified by CDER (n=155, 59.6%) and CBER (n=105, 40.4%). Sources for exposures of interest included BloodSCAN (n=39, 15.0%) and PRISM (n=66, 25.4%) for CBER, and for CDER, new molecular entities (n=30, 11.5%) and other exposures of interest (n=125, 48.1%; Appendix A). Among exposures of interest, non-intravenous medications administered by injection (injectables) were most common (n=100, 38.5%), followed by oral medications (n=91, 35.0%), and medications administered by intravenous (IV) infusion (n=53, 20.4%). Other routes of administration included inhalation, intranasal, scarification, topical, and transdermal (n=12, 5%). The majority of exposures administered by injection or IV infusion were identified by CBER, whereas oral exposures were dominated by CDER (**Figure 1**).



Nearly two-thirds of the exposures of interest are administered predominantly in outpatient settings (n=166, 63.4%). Although few are administered exclusively in inpatient settings (n=7, 2.7%), one-third (n=87, 33.5%) are administered in both outpatient and inpatient settings. Of the 95 exposures of interest administered in inpatient settings, health outcomes of interest may occur in the same inpatient stay for over half of those exposures due to a short period at risk immediately following the exposure (n=52, 54.7%). Seven exposures of interest would occur exclusively in inpatient settings; the associated health outcomes of interest would likely occur during the same hospitalization. The source for exposures of interest varied by exposure setting. The vast majority of exposures from CDER are administered predominantly in outpatient settings compared to one-quarter of exposures from CBER.





As expected, the overwhelming majority of oral exposures are likely to occur predominantly in outpatient settings. By contrast, IV infused exposures and injections might occur in either an inpatient or outpatient setting. Ten exposures of interest would likely be administered in long-term care settings, 5 would likely be administered in emergency departments, and 3 would be administered in dialysis centers.

2. Health Outcomes of Interest

With FDA, the Protocol Core reviewed and prioritized HOIs based on several factors: a) HOI has significant regulatory and/or clinical significance, b) HOI is likely to be captured within the distributed

database and it is feasible to construct an algorithm capable of reliably detecting HOI events within the distributed database, c) Likelihood that products associated with the HOI would ever have a high risk relative to a suitable control as such results will be most easily interpretable, and d) suitability of the HOI for study using epidemiologic methods (e.g., definable risk window, shorter latency periods). In addition, the Protocol Core was asked to identify clinical data elements with the potential to enhance the ascertainment of HOIs.

In total, 89 candidate HOIs were reviewed (Appendix B) related clinical data elements have been identified for 9 HOIs (shown in **Table 1**).

Table 1. Clinical Data Elements Related to Health Outcomes of Interest

HOI	Related Clinical Data Elements
Acute kidney injury[4]	Creatinine
Acute myocardial infarction (AMI)[5]	Troponin Creatine kinase-MB fraction (CK-MB)
Atrial fibrillation	Electrocardiogram results
Hypoglycemia/glucose control	Hemoglobin A1c Glucose
Lactic acidosis	Plasma lactate concentration
Neutropenia	Absolute neutrophil count (ANC)
Pancytopenia	Hemoglobin Platelets Total white count
Pulmonary hypertension	Echocardiogram results
Severe liver injury[4]	Bilirubin Albumin INR AST ALT

3. Other Priorities

In addition to identifying and prioritizing specific exposures and health outcomes of interest, other priority areas were identified including:

- Supplemental death information (cause of death) in order to accurately establish disease-specific mortality.
- Mother-infant linkage is necessary to evaluate the association between *in utero* exposure to medications and vaccines and subsequent birth outcomes.
- Linkage with state immunization registries in order to augment our current capture of vaccines.
- Linkage to registries and other networks that could be leveraged for Mini-Sentinel.
- Refinement/enhancement of existing MSCDM tables to improve their usability for Mini-Sentinel.

[4] Validation of acute kidney injury, anaphylaxis, and severe liver injury in the MSDD is currently underway.
[5] Validation of AMI was completed in May, 2011 (http://www.mini-sentinel.org/work_products/Validation_HealthOutcomes/Mini-Sentinel-Validation-of-AMI-Cases.pdf)

4. Summary

- The majority of exposures of interest occur predominantly in outpatient settings. Whereas many exposures of interest to CDER are administered orally, many exposures of interest for CBER are administered by injection or IV infusion.
- The majority of infused and injectable therapies are administered in inpatient and outpatient settings; most oral exposures occur in outpatient settings.
- Specific clinical data needs were identified for a minority of health outcomes of interest.
- Other priority areas include linkage to existing data resources that could be leveraged for Mini-Sentinel.

B. CAPTURE OF PRIORITY EXPOSURES AND HEALTH OUTCOMES OF INTEREST IN THE CURRENT MSCDM

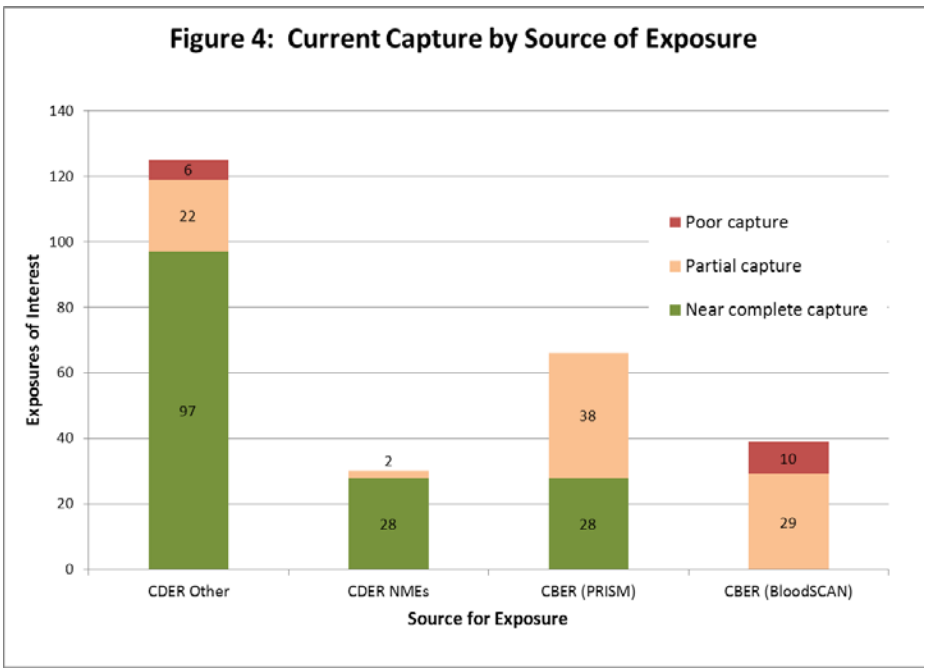
1. Exposures of Interest

Exposures are captured in the outpatient pharmacy dispensing and procedure tables of the MSCDM. Each outpatient pharmacy dispensing to a health plan member is captured in the dispensing table. Medications dispensed at discount pharmacies (e.g., Walmart, Target) may or may not be included in the table, depending on whether or not the pharmacy submits the claim to the health plan and whether the drug benefit includes dispensings at pharmacies external to the health plan. Oral medications dispensed in the inpatient setting may be captured in an inpatient EHR or other system and are not included in the dispensing table.

Infused medications, vaccinations, and other medications (e.g., injections) provided directly in outpatient or inpatient settings by medical providers are captured in the procedures table, because those administrations are considered "procedures" within the existing medical coding nomenclature. All infused or injectable therapy claims that are submitted to insurance on individual claims or recorded in outpatient EHRs within integrated delivery systems will be included in the MSDD. However, the cost of the therapy may influence whether a claim is submitted. Expensive products often require a detailed claim, but less expensive products may be bundled with other services and ambiguously captured or not captured at all in the MSDD.

For infused or injectable medications administered in outpatient settings, capture is believed to be almost complete. Capture of inpatient administrations is variable and incomplete in the local data systems of the Mini-Sentinel Data Partners, and consequently, in the MSDD. Inpatient administrations may be captured in inpatient EHRs within integrated delivery systems, but for many Data Partners, the key determinant of capture is whether claims for inpatient administrations are submitted as service-level claims or encounter-level claims (bundled). Individual exposures will not be reflected in bundled claims. Health plan contracts with hospital providers may require that service-level detail be submitted and, in such cases, inpatient administrations will be captured.

In summary, medications dispensed on an outpatient basis only are likely to be completely captured in the MSDD. Therapies that may be administered on either an inpatient or outpatient basis will be partially captured because of incomplete inpatient data capture. Therapies administered only on an inpatient basis and all blood products will be poorly captured in the MSDD.



Of the 260 exposures of interest, 153 (58.8%) are dispensed in predominantly outpatient settings and are likely to be nearly completely captured in the MSDD. Ninety-one (35.0%) are administered, in part, in inpatient settings and are only partially captured in the current MSDD, and 16 (6.2%) are administered exclusively in inpatient settings or are otherwise likely to be poorly captured (e.g., blood products).Current capture of exposures of interest to CDER is markedly higher than capture of exposures of interest to CBER. The current MSDD has near complete capture of 80.6% of exposures identified by CDER compared to 26.7% of exposures identified by CBER. The setting in which the exposures occur drives this difference: exposures of interest to CDER tend to be oral medications dispensed in outpatient settings that will have near complete capture in the current MSDD. By contrast, many exposures of interest to CBER are administered in inpatient settings where capture within the data systems of the Mini-Sentinel Data Partners is incomplete.

2. Health Outcomes of Interest

Diagnoses made during inpatient or ambulatory/outpatient encounters are captured in the diagnosis table. In general, diagnoses in the inpatient setting reflect the clinical conditions that contributed to or were germane to the inpatient stay and are based on discharge diagnoses. The number of discharge diagnoses allowed, captured, and stored on an inpatient claim varies by site, so a claim for a very complex patient may not include all recorded diagnoses. “Up coding” occurs when inpatient systems select a specific diagnosis and order the claim diagnoses to maximize reimbursement. In the outpatient setting, clinical staff or clinicians assign the diagnoses. There is usually no financial incentive to choose specific ICD-9 codes; however, there is often little incentive to code carefully. Therefore, outpatient claims tend to be less complete and the specific codes selected can be based on site specific drop-down lists, ordering, or pre-printed forms.

A variety of factors affect our ability to identify health outcomes of interest in the MSCDM.

- Some clinical conditions are complex and may be difficult to diagnose definitively (e.g. transfusion related acute lung injury). If clinicians are reluctant to make a definitive diagnosis, complex clinical conditions may be under-coded in claims.

- The condition may not be accurately reflected by the available ICD-9 codes and therefore identifying such health conditions requires using surrogate codes and algorithms that approximate the health outcome of interest (e.g. acute hemolytic reaction or hemolysis).
- New codes can be introduced and some codes are discontinued, making longitudinal analysis more complex.
- Coding patterns can change over time and vary by Data Partner, which can introduce complexity in defining HOIs.
- Combinations or sequences of diagnosis codes based on algorithms may be necessary to identify HOIs.
- Some HOI definitions may require procedure and even drug codes in addition to diagnosis codes, introducing additional complexity in consistently defining HOIs across Partners and over time.
- Not all code types are captured across all Data Partners. The codes necessary to identify suicide or other external causes of injury (e.g., E-codes in the ICD-9-CM), for example, are inconsistently available.
- Length of follow-up is an issue for outcomes with a long latency period.

Additionally, clinical or laboratory data may be necessary to definitively establish a diagnosis. **Table 2** shows the current capture of clinical data related to the 9 priority HOIs described earlier.

Table 2. Current Capture of Clinical Data Elements Related to Health Outcomes of Interest

HOI	Potential Data Needs	Current MSCDM
Acute kidney injury	Creatinine	Creatinine was among the outpatient labs included in the Year 2 clinical data enhancements. Inpatient labs are not currently available.
Acute myocardial infarction (AMI)	Troponin Creatine kinase-MB fraction (CK-MB)	Troponin and CK-MB are among the outpatient labs included in the Year 3 clinical data enhancements. Inpatient labs are not currently available.
Atrial fibrillation	Electrocardiogram results	Not currently available.
Hyperglycemia/glucose control	Hemoglobin A1c (HbA1c) Glucose	HbA1c and glucose were among the outpatient labs included in the Year 2 clinical data enhancements. Inpatient labs are not currently available.
Lactic acidosis	Plasma lactate concentration	Not currently available.
Neutropenia	Absolute neutrophil count (ANC)	Outpatient ANC was included in the Year 2 clinical data enhancements. Inpatient labs are not currently available.
Pancytopenia	Hemoglobin Platelets Total white count	Hemoglobin was among the outpatient labs included in the Year 2 enhancements; platelets were included in the Year 3 enhancements. Inpatient labs are not currently available.
Pulmonary hypertension	Echocardiogram results	Not currently available.
Severe liver injury	Bilirubin Albumin INR AST ALT	Total bilirubin and INR were among the outpatient labs included in the Year 2 clinical data enhancements. Albumin is not currently available. Inpatient labs are not currently available.

3. Other Priorities

- **Supplemental death information (cause of death):**
  The Data Partners have various mechanisms for acquiring information about an enrollee's death. If a patient dies while in the hospital, the death is recorded in association with a related discharge disposition. However, many patients die outside the clinical setting and the only clue to the death is the cessation of health utilization activity. Therefore, to confirm the death, half of the Data Partners link to local (state) death registries to update the death status and identify cause of death of their members. Cause of death is obtained for a minority of members. As of July 2012, approximately 3.5 million individuals were included in the death table but only 1.2 million had a corresponding cause of death record. Linkage to local (state) death registries is performed relatively infrequently—about once a year for most Data Partners. As a result, a two-year lag in death data is not uncommon.

- **Mother-infant linkage:**
  The current MSCDM does not include the necessary data elements/files to evaluate the safety of medications and vaccines in pregnant women. A collaborative pilot research program, the Medication Use in Pregnancy and Birth Outcomes Program (MEPREP), between the Food and Drug Administration (FDA) and researchers at the HMO Research Network Center for Education and Research in Therapeutics (CERT), Kaiser Permanente Northern and Southern California, and Vanderbilt University, has developed common, necessary data linkages and developed standard data files to enable the conduct of multiple studies of medication use and outcomes in pregnancy across participating sites.[6] Specific potential additions for Mini-Sentinel include: (1) A file linking mothers and infants for all women delivering an infant (including such variables as baby id, mother id, baby date of birth, and possibly method of linkage (e.g., family contract number, registry, name/address, birth certificate) and (2) birth certificate data for infants. (An ongoing Mini-Sentinel workgroup activity is underway to address the feasibility of obtaining birth information from select states for PRISM Data Partners.)

- **State Vaccine Table:**
  In Year Three, PRISM Data Partners linked health plan members with state-based immunization registries to create a State Vaccine Table. Specifically, the table captures vaccine exposure information including code, date, manufacturer and lot number (when available). Vaccine information from the Data Partner claims data and the registry were retained and de-duplicated based on vaccine specific information and the data. The State Vaccine Table is being incorporated into the MSCDM, but only 3 Data Partners are contributing the linked immunization registry data.

- **Linkage to registries and other networks and data systems:**
  Professional societies and research organizations have developed registries that collect uniform, often detailed data for a population defined by a disease, exposure, or event. Linkage with these existing data resources would augment the data resources available to FDA by leveraging the substantial development work that other groups have undertaken.

[6] MEPREP is funded through a separate contract with CDER and is not part of Mini-Sentinel.

- **Refinements to current MSCDM tables:**
  In addition to the new data areas described above, several potential refinements to current MSCDM tables have been identified by the MSOC, MS investigators and MS Data Partners.

  - Flag that indicates whether enrollee data are available for chart abstraction:
    For large Data Partners in particular, not all enrollee data are available for chart abstraction. For example, claims data for enrollees in Administrative Services Only (ASO) plans will be reflected in the MSDD, but data for chart abstraction would not be available. Inclusion of the flag would improve the efficiency of chart validation studies by limiting the sampling frame to those enrollees for whom enrollee data are available.
  - Plan type (Administrative Services Only [ASO], Preferred Provider Organization [PPO], Point of Service [POS], etc):
    A variety of plan types are represented among the MS Data Partners and, in some cases, the type of plan determines the granularity of the available data. A plan indicator variable could inform our understanding of the quality and completeness of the MSDD.
  - Primary/secondary insurance indicators:
    Enrollees may be covered by multiple health plans and insurers which could, in turn, contribute to systematic incomplete capture of information about exposures and outcomes of interest. An indicator that signifies whether the health plan is the primary or secondary insurer would help to identify members for whom we expect complete capture of medical and drug usage.
  - Patient 5-digit ZIP code:
    Sociodemographic factors may confound observed associations between exposures and outcomes. Incorporation of patient ZIP code would facilitate the incorporation of ZIP code-based measures of sociodemographic factors (e.g., income, education), by enabling linkage to census data organized by ZIP code.
  - Specialty of service provider:
    The specialty of the service provider has the potential to inform our interpretation of diagnosis codes observed in the MSDD. For example, a diagnosis of acute kidney injury on a claim filed by a nephrologist may have a higher positive predictive value than the same diagnosis on a claim filed by a podiatrist.
  - Unique Device Identification (UDI):
    FDA has released a proposed rule that most medical devices distributed in the United States carry a unique device identifier (UDI). A UDI is specific to a device model and a production identifier (lot or batch number, serial number and/or expiration date). Inclusion of the UDI in the MSCDM procedure table would enable the MSDD to support evaluations of device-based therapies.

4. Summary

Several gaps exist in the current MSCDM with respect to identified priorities.

- Capture of inpatient administrations is variable and incomplete. Although many exposures of interest to CDER occur predominantly in outpatient settings, inpatient administrations are not uncommon. Additionally, exposures of interest to CBER include blood products and products that are administered, in part, in inpatient settings. CDER and CBER have strong interests in developing the ability to assess the safety of medications given primarily in the inpatient setting.

- Inpatient laboratory data related to inpatient diagnoses of several health outcomes of interest are not included in the current MSCDM.
- Cause of death is not available for two-thirds of the Mini-Sentinel population.
- Infants and mothers are not linked so evaluations of the safety of medications and vaccines in pregnant women cannot currently be undertaken.
- The opportunities to leverage existing data resources for Mini-Sentinel have not been fully explored.

C. RECOMMENDATIONS FOR ADDRESSING GAPS IN THE MSCDM

The development of new data sources to address gaps in the MSCDM requires careful consideration. For each identified gap, we briefly present a recommendation and rationale and, if appropriate, an approach and preliminary assessment of risks and likelihood of success.

1. Access to Inpatient Data Streams

- *Recommendation:* Partner with a national hospital-based organization to access inpatient data streams.
- *Rationale:* Encounter-level inpatient claims received by many of the large Data Partners do not enable us to identify specific inpatient administrations. Moreover, inpatient data streams are available for a minority of Data Partners accounting for less than 10% of enrollees in the MSDD. Rather than invest the significant time and resources to develop internal inpatient data sources, an alternative approach is to partner with a national hospital-based organization and develop inpatient table(s) for the MSCDM from their data sources. Initial assessments would focus on exposure-outcome pairs likely to occur during the same inpatient stay. As cross-institutional linkages are developed, exposure-outcome pairs could cross settings.
- *Approach:* 1-year feasibility assessment (to be conducted in stages). Key issues to address include (1) capture and completeness of specific inpatient data elements of interest (i.e., exposures, lab data to support selected inpatient diagnoses), (2) overlap of network hospitals with MS Data Partner hospital sites, (3) availability of necessary data elements for linkage, and (4) methods to perform patient-level matching and linking.
- *Assessment of risks and likelihood of success:* Cross-institutional linkages are challenging so the data might only be useful for exposure-outcome pairs that occur within the same inpatient stay. Of note, Optum Insight is in the early phase of an FDA-funded project that will link their claims-type data with inpatient data from Premier. Results from that project will inform our feasibility assessment.
- *Proposed Priority:* High

2. Cause of Death Data

- *Recommendation:* Do not pursue supplemental death information at this time, but reconsider if the timeliness of the data improves substantially.
- *Rationale:* Release of cause of death data from the National Death Index is not timely and currently lags by 2 years.
- *Proposed Priority:* Low

3. Mother-infant Linkage

- *Recommendation:* Expand the MSCDM to support mother-infant linkage.
- *Rationale:* Evaluating the safety of medications and vaccines in pregnant women requires linkage between mothers and infants. The recommendation leverages an ongoing collaborative pilot research program, the Medication Use in Pregnancy and Birth Outcomes Program (MEPREP), between the FDA and researchers at the HMO Research Network Center for Education and Research in Therapeutics (CERT), Kaiser Permanente Northern and Southern California, and Vanderbilt University. An ongoing Mini-Sentinel workgroup activity is underway to address the feasibility of obtaining information from select states for PRISM Data Partners.
- *Approach:* Based on the ongoing feasibility assessment, incorporate (1) a file linking mothers and infants for all women delivering an infant (including such variables as baby id, mother id, baby date of birth, and possibly method of linkage (e.g., family contract number, registry, name/address, birth certificate) and (2) birth certificate data for infants (1-year feasibility assessment to be conducted in stages) into the MSCDM.
- *Assessment of risks and likelihood of success:* Given the substantial development work undertaken by the MEPREP team, the likelihood of success is high.
- *Proposed Priority:* High

4. State Vaccine Table

- *Recommendation:* Complete incorporation of the state vaccine table in the MSCDM and expand number of Data Partners who complete the linkage.
- *Rationale:* Inclusion of the state vaccine table into the MSCDM will standardize the structure of the data table and enable other Data Partners to populate the tables for broader use.
- *Approach:* Pending internal review of the table specifications for clarity, add the table to the next iteration (v4) of the MSCDM and expand the number of Data Partners who populate the table.
- *Assessment of risks and likelihood of success:* Given the substantial development work undertaken by PRISM, the likelihood of success is high.
- *Proposed Priority:* Medium

5. Linkage to Registries and Other Networks

- *Recommendation:* Explore the possibility of leveraging existing data networks and registries in Mini-Sentinel.
- *Rationale:* Professional societies and research groups have committed substantial resources to the development and maintenance of registries and data networks. These resources often have richer clinical details than available within Mini-Sentinel, and can include other details not available within the MSDD. Leveraging these resources could quickly augment the data resources available to FDA by providing detailed data for a population with a specific disease, exposure, or event.
- *Approach:* Compile a comprehensive list of data networks and registries and assess their ability to augment current MS data resources. Factors to consider include (1) capture and completeness of specific data elements of interest, 2) overlap of sites with MS Data Partner enrollees, and (3) availability of unique data elements unavailable within the MSCDM. The proposed compilation might be similar in scope to the report on complementary data sources

developed by the PRISM team.[7]

- *Assessment of risks and likelihood of success:* The feasibility assessment has minimal risks and will inform future expansion decisions.
- *Proposed Priority:* Medium

6. Refinements to Current MSCDM Tables

- *Recommendation:* Revise the current MSCDM tables to include (1) a flag that indicates whether data are available for chart abstraction; (2) patient 5-digit ZIP code; and (3) the Unique Device Identifier (UDI).
- *Rationale:* A flag that indicates whether data are available for chart abstraction will improve the efficiency of validation studies, patient 5-digit ZIP code will facilitate the incorporation of ZIP code-based measures of sociodemographic factors as confounders, and the UDI will facilitate device-based evaluations. Data Partners advised against the incorporation of plan indicators or primary/secondary insurance indicators. Standardizing plan definitions would be time-consuming and definitions change over time. Similarly, the determination of primary vs. secondary insurance is often made on a patient-by-patient basis. Availability and reliability of physician specialty across Data Partners should be established before its inclusion in the MSCDM.
- *Approach:* Add indicator flag for chart abstraction and 5-digit patient ZIP code to the enrollment table.
- *Assessment of risks and likelihood of success:* Incorporation of the additional data elements carries minimal risks.
- *Proposed Priority:* High

[7] http://www.mini-sentinel.org/work_products/Data_Activities/Mini-Sentinel_PRISM_Identifying-Complementary-Data-Sources-Report.pdf

IV. APPENDIX A. MASTER LIST OF EXPOSURES

Source	Exposure(s)	Route of Administration	Setting	Capture
CDER NMEs	abiraterone acetate	Oral	Predominantly OP	Near complete capture
CDER NMEs	aflibercept	Injection	Predominantly OP	Near complete capture
CDER NMEs	asparaginase, Erwinia, chrysanthemi	Injection	Predominantly OP	Near complete capture
CDER NMEs	azilsartan medoxomil	Oral	Predominantly OP	Near complete capture
CDER NMEs	belatacept	IV infusion	IP and OP	Partial capture
CDER NMEs	belimumab	Injection	Predominantly OP	Near complete capture
CDER NMEs	boceprevir	Oral	Predominantly OP	Near complete capture
CDER NMEs	brentuximab vedotin	Injection	Predominantly OP	Near complete capture
CDER NMEs	clobazam	Oral	Predominantly OP	Near complete capture
CDER NMEs	crizotinib	Oral	Predominantly OP	Near complete capture
CDER NMEs	deferiprone	Oral	Predominantly OP	Near complete capture
CDER NMEs	ezogabine	Oral	Predominantly OP	Near complete capture
CDER NMEs	fidaxomicin	Oral	Predominantly OP	Near complete capture
CDER NMEs	gabapentin enacarbil	Oral	Predominantly OP	Near complete capture
CDER NMEs	gadobutrol	Injection	Predominantly OP	Near complete capture
CDER NMEs	icatibant	Injection	Predominantly OP	Near complete capture
CDER NMEs	indacaterol inhalation powder	Oral	Predominantly OP	Near complete capture
CDER NMEs	ioflupane i-123	Injection	Predominantly OP	Near complete capture
CDER NMEs	Ipilimumab (Yervoy)	IV infusion	Predominantly OP	Near complete capture
CDER NMEs	linagliptin	Oral	Predominantly OP	Near complete capture
CDER NMEs	rilpivirine	Oral	Predominantly OP	Near complete capture
CDER NMEs	rivaroxaban	Oral	Predominantly OP	Near complete capture
CDER NMEs	roflumilast	Oral	IP and OP	Partial capture
CDER NMEs	ruxolitinib	Oral	Predominantly OP	Near complete capture
CDER NMEs	spinosad	Topical	Predominantly OP	Near complete capture
CDER NMEs	telaprevir	Oral	Predominantly OP	Near complete capture
CDER NMEs	ticagrelor	Oral	Predominantly OP	Near complete capture
CDER NMEs	vandetanib	Oral	Predominantly OP	Near complete capture
CDER NMEs	vemurafenib	Oral	Predominantly OP	Near complete capture
CDER NMEs	vilazodone HCL	Oral	Predominantly OP	Near complete capture
CDER Other	4-AMINOPYRIDINE EXTENDED RELEASE, DALFAMPRIDINE, FAMPRIDINE SR, AMPYRA 10MG BID	Oral	Predominantly OP	Near complete capture
CDER Other	ACE INHIBITOR	Oral	Predominantly OP	Near complete capture
CDER Other	Actemra (tocilizumab)	IV infusion	Predominantly OP	Near complete capture
CDER Other	ALEFACEPT (AMEVIVE)	Injection	Predominantly OP	Near complete capture
CDER Other	ALISKIREN	Oral	Predominantly OP	Near complete capture
CDER Other	alpha interferons	Injection	IP and OP	Partial capture
CDER Other	ANESTHETIC DRUG PRODUCTS	Injection	IP and OP	Poor capture
CDER Other	ANTIDEPRESSANTS	Oral	Predominantly OP	Near complete capture
CDER Other	ANTIEPILEPTIC DRUGS	Oral	Predominantly OP	Near complete capture
CDER Other	APOKYN	Injection	Predominantly OP	Partial capture
CDER Other	ARICEPT (DONEPEZIL HCL)	Oral	Predominantly OP	Partial capture

Source	Exposure(s)	Route of Administration	Setting	Capture
	TABLETS			
CDER Other	ATYPICAL ANTIPSYCHOTICS	Oral	Predominantly OP	Partial capture
CDER Other	AZILECT (RASAGILINE)	Oral	Predominantly OP	Partial capture
CDER Other	BENZOCAINE	Topical	Predominantly OP	Near complete capture
CDER Other	bevacizumab	IV infusion	IP and OP	Near complete capture
CDER Other	Byetta (exenatide)	Injection	Predominantly OP	Near complete capture
CDER Other	Cancidas (caspofungin)	IV infusion	IP and OP	Partial capture
CDER Other	CETUXIMAB (ERBITUX, IMCLONE)	Injection	Predominantly OP	Near complete capture
CDER Other	CITALOPRAM HYDROBROMIDE TABLETS 10/20/40	Oral	Predominantly OP	Near complete capture
CDER Other	Clevidipine	Injection	IP and OP	Partial capture
CDER Other	CLOMIPHENE CITRATE TABLETS	Oral	Predominantly OP	Near complete capture
CDER Other	CLOZAPINE	Oral	Predominantly OP	Near complete capture
CDER Other	CORTICOSTEROIDS	Oral	Predominantly OP	Near complete capture
CDER Other	CYMBALTA(DULOXETINE HCL)20,30,40,6OMG	Oral	Predominantly OP	Near complete capture
CDER Other	DABIGATRAN ETEXILATE MESYLATE	Oral	Predominantly OP	Near complete capture
CDER Other	Denosumab (Prolia)	Injection	Predominantly OP	Near complete capture
CDER Other	DEPAKENE (VALPROIC ACID)	Oral	Predominantly OP	Near complete capture
CDER Other	DEPAKOTE (DIVALPROEX SODIUM)	Oral	Predominantly OP	Near complete capture
CDER Other	DILANTIN (PHENYTOIN) INJECTION	Oral	Predominantly OP	Near complete capture
CDER Other	DILANTIN (PHENYTOIN) INJECTION	IV infusion	IP and OP	Partial capture
CDER Other	DIPEPTIDYL PEPTIDASE IV(DPP-IV)INHIBITOR (gliptins)	Oral	Predominantly OP	Near complete capture
CDER Other	DOPAMINE AGONISTS	Oral	Predominantly OP	Partial capture
CDER Other	DROSPIRENONE/EHTINYL ESTRADIOL	Oral	Predominantly OP	Near complete capture
CDER Other	Ecallantide (Kalbitor)	Injection	IP and OP	Partial capture
CDER Other	EFFEXOR (VENLAFAXINE HCL) TABLETS	Oral	Predominantly OP	Near complete capture
CDER Other	EMSAM (SELEGILINE TRANSDERMAL SYSTEM)	Transdermal	Predominantly OP	Near complete capture
CDER Other	ENBREL (ETANERCEPT)	Injection	Predominantly OP	Near complete capture
CDER Other	ENTEREG (ALVIMOPAN)	Oral	IP only	Poor capture
CDER Other	EPOETIN ALFA (PROCRIT) AND DARBEPOETIN ALFA (ARANESP)	Injection	Predominantly OP	Poor capture
CDER Other	Eribulin mesylate (Halaven)	IV Infusion	Predominantly OP	Near complete capture
CDER Other	EVEROLIMUS	Oral	Predominantly OP	Near complete capture
CDER Other	FINGOLIMOD HCL ORAL CAPSULES	Oral	Predominantly OP	Partial capture
CDER Other	FLUOROQUINOLONE CLASS	Oral	Predominantly OP	Near complete capture
CDER Other	GEODON (ZIPRASIDONE HCL)	Oral	Predominantly OP	Near complete capture

Source	Exposure(s)	Route of Administration	Setting	Capture
CDER Other	GnRH analogs	Injection	Predominantly OP	Near complete capture
CDER Other	GONADOTROPIN-RELEASING HORMONE (GNRH) AGONISTS	Injection	Predominantly OP	Near complete capture
CDER Other	HIV PROTEASE INHIBITORS	Oral	Predominantly OP	Near complete capture
CDER Other	HMG-COA REDUCTASE INHIBITORS	Oral	Predominantly OP	Near complete capture
CDER Other	HORIZANT	Oral	Predominantly OP	Near complete capture
CDER Other	HUMAN ERYTHROPOIETIN (RECOMBINANT, CHO CELLS)	IV infusion	Predominantly OP	Partial capture
CDER Other	HUMATROPE	Injection	Predominantly OP	Near complete capture
CDER Other	HUMIRA (ADALIMUMAB)	Injection	Predominantly OP	Near complete capture
CDER Other	ILOPROST INHALATION SOLUTION (VENTAVIS)	Inhaled	Predominantly OP	Near complete capture
CDER Other	INFLIXIMAB (REMICADE)	IV infusion	Predominantly OP	Near complete capture
CDER Other	Insulin glargine (Lantus)	Injection	Predominantly OP	Near complete capture
CDER Other	INTERFERON ALFAS	Injection	Predominantly OP	Near complete capture
CDER Other	INTERFERON ALPHA-2B (INTRON-A, SCHERING), PEGINTEFERON ALFA-2B (PEGINTRON, SCHERING	Injection	Predominantly OP	Near complete capture
CDER Other	Ipilimumab (Yervoy)	IV Infusion	Predominantly OP	Near complete capture
CDER Other	Iron dextran (Dexferrum) Iron dextran (Infed) Iron dextran (Iron Dextran) Iron dextran (Proferdex) Iron Sucrose (Venofer)	IV infusion	IP and OP	Partial capture
CDER Other	ISENTRESS (RALTEGRAVIR)	Oral	Predominantly OP	Near complete capture
CDER Other	IVACAFTOR	Oral	Predominantly OP	Near complete capture
CDER Other	Keppra (levetiracetam)	Oral	Predominantly OP	Near complete capture
CDER Other	Keppra (levetiracetam)	IV infusion	IP only	Poor capture
CDER Other	KRYSTEXXA (PEGLOTICASE)	Injection	IP and OP	Poor capture
CDER Other	Liraglutide (Victoza)	Injection	Predominantly OP	Near complete capture
CDER Other	LOCAL ANESTHETICS	Injection	IP and OP	Partial capture
CDER Other	LUMIZYME (ALGLUCOSIDASE ALFA)	IV infusion	Predominantly OP	Near complete capture
CDER Other	MACROLIDE CLASS	Oral	Predominantly OP	Near complete capture
CDER Other	METHERGINE	Oral	Predominantly OP	Near complete capture
CDER Other	METHERGINE	Injection	Predominantly OP	Near complete capture
CDER Other	METHERGINE	IV infusion	IP and OP	Partial capture
CDER Other	Miacalcin/Fortical (calcitonin)	Intranasal	Predominantly OP	Near complete capture
CDER Other	Miacalcin/Fortical (calcitonin)	Injection	Predominantly OP	Near complete capture
CDER Other	Mycamine (micafungin)	IV infusion	IP and OP	Partial capture
CDER Other	NAMENDA XR(MEMANTINE HCL)ER CAPSULES	Oral	Predominantly OP	Partial capture
CDER Other	Natalizumab (Tysabri)	Injection	Predominantly OP	Near complete capture
CDER Other	NEXAVAR (SORAFENIB)	Oral	Predominantly OP	Near complete capture
CDER Other	NILOTINIB (TASIGNA)	Oral	Predominantly OP	Near complete capture

Source	Exposure(s)	Route of Administration	Setting	Capture
CDER Other	NIZORAL (KETOCONAZOLE)	Oral	Predominantly OP	Near complete capture
CDER Other	NON-STEROIDAL ANTI-INFLAMMATORY DRUGS (NSAIDS)	Oral	Predominantly OP	Near complete capture
CDER Other	NOVANTRONE (MITOXANTRONE)	IV infusion	IP and OP	Partial capture
CDER Other	NUCYNTA (TAPENTADOL) IMMEDIATE-RELEASE TABLETS	Oral	Predominantly OP	Near complete capture
CDER Other	Orencia (abacept)	IV infusion	Predominantly OP	Near complete capture
CDER Other	ORTHO EVRA(NORELGESTROMIN/ETHINYL ESTRAD	Oral	Predominantly OP	Near complete capture
CDER Other	OVIDE	Topical	Predominantly OP	Near complete capture
CDER Other	OXYCONTIN (OXYCODONE HCL) CR TABS	Oral	Predominantly OP	Near complete capture
CDER Other	PARLODEL	Oral	Predominantly OP	Near complete capture
CDER Other	Plenaxis (Abarelix)	Injection	Predominantly OP	Near complete capture
CDER Other	PLENAXIS DEPOT (ABARELIX) DEPOT SUSPENSI	Injection	Predominantly OP	Near complete capture
CDER Other	Polidicanol (Asclera)	Injection	Predominantly OP	Near complete capture
CDER Other	PREMARIN TABLETS	Oral	Predominantly OP	Near complete capture
CDER Other	PROTON PUMP INHIBITORS	Oral	Predominantly OP	Near complete capture
CDER Other	PROVIGIL (MODAFINIL)	Oral	Predominantly OP	Near complete capture
CDER Other	PROVIGIL (MODAFINIL) / NUVIGIL (ARMODAFINIL)	Oral	Predominantly OP	Near complete capture
CDER Other	PROZAC (FLUOXETINE)	Oral	Predominantly OP	Near complete capture
CDER Other	recombinant human growth hormones	Injection	Predominantly OP	Near complete capture
CDER Other	REGRANEX (BECAPLERMIN) GEL	Topical	Predominantly OP	Near complete capture
CDER Other	RIBAVIRIN	Oral	Predominantly OP	Near complete capture
CDER Other	Romidepsin (Stodax, Istodax)	IV infusion	Predominantly OP	Near complete capture
CDER Other	SABRIL (VIGABATRIN)	Oral	Predominantly OP	Near complete capture
CDER Other	Sandostatin (octreotide)	Injection	Predominantly OP	Near complete capture
CDER Other	SAPHRIS (ASENAPINE) SUBLINGUAL TABLETS	Oral	Predominantly OP	Partial capture
CDER Other	SELECTIVE SEROTONIN REUPTAKE INHIBITORS	Oral	Predominantly OP	Near complete capture
CDER Other	SILDENAFIL	Oral	Predominantly OP	Near complete capture
CDER Other	SINGULAIR (MONTELUKAST)	Oral	Predominantly OP	Near complete capture
CDER Other	Sorafenib	Oral	Predominantly OP	Near complete capture
CDER Other	STALEVO (CARBIDOPA/LEVODOPA/ENTACAPONE)	Oral	Predominantly OP	Partial capture
CDER Other	SYMLIN (PRAMLINTIDE ACETATE) INJECTION	Injection	Predominantly OP	Near complete capture
CDER Other	TAMIFLU 75 MG CAPSULES	Oral	Predominantly OP	Near complete capture
CDER Other	Cimzia (certolizumab)	Injection	Predominantly OP	Near complete capture

Source	Exposure(s)	Route of Administration	Setting	Capture
CDER Other	Simponi (golimumab)	Injection	Predominantly OP	Near complete capture
CDER Other	TOPAMAX (TOPIRAMATE)	Oral	Predominantly OP	Near complete capture
CDER Other	TRAMADOL HYDROCHLORIDE	Oral	Predominantly OP	Near complete capture
CDER Other	TRIPTANS (5-HT 1B/1D AGONISTS)	Oral	Predominantly OP	Near complete capture
CDER Other	TYROSINE KINASE INHIBITORS	Oral	Predominantly OP	Near complete capture
CDER Other	Ustekinumab (Stelara)	Injection	Predominantly OP	Near complete capture
CDER Other	VANDETANIB	Oral	Predominantly OP	Near complete capture
CDER Other	VIMPAT (LACOSAMIDE)	Oral	Predominantly OP	Near complete capture
CDER Other	VIMPAT (LACOSAMIDE)	IV infusion	IP only	Poor capture
CDER Other	VIREAD (TENOFOVIR)	Oral	Predominantly OP	Near complete capture
CDER Other	XENAZINE (TETRABENAZINE)	Oral	Predominantly OP	Partial capture
CDER Other	XENICAL (ORLISTAT)	Oral	Predominantly OP	Near complete capture
CDER Other	ZIAGEN	Oral	Predominantly OP	Near complete capture
CDER Other	Zoledronic acid (Reclast)	Injection	IP and OP	Partial capture
CDER Other	ZYCLARA (IMIQUIMOD) CREAM 3.75%	Topical	Predominantly OP	Near complete capture
CBER BloodSCAN	Cryoprecipitated AHF	IV Infusion	IP only	Poor capture
CBER BloodSCAN	Plasma	IV Infusion	IP only	Poor capture
CBER BloodSCAN	Platelets	IV Infusion	IP and OP	Poor capture
CBER BloodSCAN	Platelets leukoreduced	IV Infusion	IP and OP	Poor capture
CBER BloodSCAN	Platelets irradiated	IV Infusion	IP and OP	Poor capture
CBER BloodSCAN	Platelets leukoreduced and irradiated	IV Infusion	IP and OP	Poor capture
CBER BloodSCAN	Red Blood Cells	IV Infusion	IP and OP	Poor capture
CBER BloodSCAN	Red Blood Cells leukoreduced	IV Infusion	IP and OP	Poor capture
CBER BloodSCAN	Red Blood Cells irradiated	IV Infusion	IP and OP	Poor capture
CBER BloodSCAN	Red Blood Cells leukoreduced and irradiated	IV Infusion	IP and OP	Poor capture
CBER BloodSCAN	NovoSeven RT	IV Infusion	IP only	Partial capture
CBER BloodSCAN	Advate	IV Infusion	IP and OP	Partial capture
CBER BloodSCAN	Alphanate, Profilate	IV Infusion	IP and OP	Partial capture
CBER BloodSCAN	Hemofil, Hemofil M, Method M, Monarc-M	IV Infusion	IP and OP	Partial capture
CBER BloodSCAN	Humate-P	IV Infusion	IP and OP	Partial capture
CBER BloodSCAN	Koate, Koate-DVI	IV Infusion	IP and OP	Partial capture
CBER BloodSCAN	Kogenate, Kogenate FS, Helixate, Helixate FS	IV Infusion	IP and OP	Partial capture
CBER BloodSCAN	Monoclate, Monoclate-P	IV Infusion	IP and OP	Partial capture
CBER BloodSCAN	Recombinate, Bioclate	IV Infusion	IP and OP	Partial capture
CBER BloodSCAN	ReFacto	IV Infusion	IP and OP	Partial capture
CBER BloodSCAN	Xyntha	IV Infusion	IP and OP	Partial capture
	Wilate	IV infusion		
CBER BloodSCAN	Carimune, Carimune Nf, Panglobulin, Panglobulin Nf, Sandoglobulin, Zlb Immune Globulin Intravenous (Human),	IV Infusion	IP and OP	Partial capture

Source	Exposure(s)	Route of Administration	Setting	Capture
	[Redimune]			
CBER BloodSCAN	Gammagard S/D	IV Infusion	IP and OP	Partial capture
CBER BloodSCAN	Flebogamma 5% DIF, Flebogamma 10% DIF	IV Infusion	IP and OP	Partial capture
CBER BloodSCAN	Gammagard Liquid, [Kiovig]	IV Infusion	IP and OP	Partial capture
CBER BloodSCAN	Gammagard Liquid, [Kiovig]	Injection	IP and OP	Partial capture
CBER BloodSCAN	Gammaplex	IV Infusion	IP and OP	Partial capture
CBER BloodSCAN	Gamunex-C, Gammaked, [IGIV-C]	IV Infusion	IP and OP	Partial capture
CBER BloodSCAN	Gamunex-C, Gammaked, [IGIV-C]	Injection	IP and OP	Partial capture
CBER BloodSCAN	Hizentra	Injection	Predominantly OP	Partial capture
CBER BloodSCAN	Octagam	IV Infusion	IP and OP	Partial capture
CBER BloodSCAN	Privigen	IV Infusion	IP and OP	Partial capture
CBER BloodSCAN	Vivaglobin	Injection	Predominantly OP	Partial capture
CBER BloodSCAN	HepaGam B	IV Infusion	IP and OP	Partial capture
CBER BloodSCAN	HepaGam B	Injection	IP and OP	Partial capture
CBER BloodSCAN	Berinert	IV Infusion	IP and OP	Partial capture
CBER BloodSCAN	Cinryze	IV Infusion	IP and OP	Partial capture
CBER BloodSCAN	HyperTET	IV Infusion	IP only	Partial capture
CBER BloodSCAN	GamaSTAN, GamaSTAN S/D	IV Infusion	IP and OP	Partial capture
CBER PRISM	Acam2000	Scarification	Predominantly OP	Near complete capture
CBER PRISM	Adacel	Injection	IP and OP	Partial capture
CBER PRISM	Adenovirus (Types 4 and 7), Live, Oral	Oral	Predominantly OP	Near complete capture
CBER PRISM	Afluria	Injection	IP and OP	Partial capture
CBER PRISM	Agriflu	Injection	IP and OP	Partial capture
CBER PRISM	Attenuvax	Injection	Predominantly OP	Near complete capture
CBER PRISM	Biothrax	Injection	Predominantly OP	Near complete capture
CBER PRISM	Boostrix	Injection	IP and OP	Partial capture
CBER PRISM	Cervarix	Injection	Predominantly OP	Near complete capture
CBER PRISM	Comvax	Injection	IP and OP	Partial capture
CBER PRISM	Daptacel	Injection	IP and OP	Partial capture
CBER PRISM	Decavac	Injection	IP and OP	Partial capture
CBER PRISM	Menhiberix	Injection	Predominantly OP	Near complete capture
CBER PRISM	DTaP	Injection	IP and OP	Partial capture
CBER PRISM	Diphtheria & Tetanus Toxoids Adsorbed	Injection	IP and OP	Partial capture
CBER PRISM	Tetanus Toxoid Adsorbed	Injection	IP and OP	Partial capture
CBER PRISM	Fluzone ID	Injection	IP and OP	Partial capture
CBER PRISM	Flucelvax	Injection	IP and OP	Partial capture
CBER PRISM	Engerix-B	Injection	Predominantly OP	Near complete capture
CBER PRISM	Fluarix	Injection	IP and OP	Partial capture
CBER PRISM	FluLaval	Injection	IP and OP	Partial capture
CBER PRISM	FluMist	Intranasal	IP and OP	Partial capture
CBER PRISM	FluVirin	Injection	IP and OP	Partial capture
CBER PRISM	Fluzone	Injection	IP and OP	Partial capture

Source	Exposure(s)	Route of Administration	Setting	Capture
CBER PRISM	Fluzone HD	Injection	IP and OP	Partial capture
CBER PRISM	Gardasil	Injection	Predominantly OP	Near complete capture
CBER PRISM	Havrix	Injection	Predominantly OP	Near complete capture
CBER PRISM	Hiberix	Injection	Predominantly OP	Near complete capture
CBER PRISM	Imovax Rabies	Injection	IP and OP	Partial capture
CBER PRISM	Infanrix	Injection	IP and OP	Partial capture
CBER PRISM	IPOL	Injection	IP and OP	Partial capture
CBER PRISM	Ixiaro	Injection	Predominantly OP	Near complete capture
CBER PRISM	JE-Vax	Injection	Predominantly OP	Near complete capture
CBER PRISM	Kinrix	Injection	IP and OP	Partial capture
CBER PRISM	Flumist	Intranasal	IP and OP	Partial capture
CBER PRISM	Menactra	Injection	Predominantly OP	Near complete capture
CBER PRISM	Menomune	Injection	Predominantly OP	Near complete capture
CBER PRISM	Menveo	Injection	Predominantly OP	Near complete capture
CBER PRISM	Meruvax II	Injection	Predominantly OP	Near complete capture
CBER PRISM	M-M-R II	Injection	IP and OP	Partial capture
CBER PRISM	MumpsVax	Injection	Predominantly OP	Near complete capture
CBER PRISM	OmniHib/ActHIB	Injection	Predominantly OP	Near complete capture
CBER PRISM	Pediarix	Injection	IP and OP	Partial capture
CBER PRISM	PedVaxHib	Injection	IP and OP	Partial capture
CBER PRISM	Pentacel	Injection	IP and OP	Partial capture
CBER PRISM	Pneumovax 23	Injection	IP and OP	Partial capture
CBER PRISM	Poliovax	Injection	IP and OP	Partial capture
CBER PRISM	Prevnar13	Injection	IP and OP	Partial capture
CBER PRISM	Prevnar7	Injection	IP and OP	Partial capture
CBER PRISM	ProQuad	Injection	Predominantly OP	Near complete capture
CBER PRISM	RabAvert	Injection	IP and OP	Partial capture
CBER PRISM	Recombivax/Recombivax HB	Injection	Predominantly OP	Near complete capture
CBER PRISM	Rotarix	Oral	IP and OP	Partial capture
CBER PRISM	Rotateq	Oral	IP and OP	Partial capture
CBER PRISM	Tenivac	Injection	IP and OP	Partial capture
CBER PRISM	TIV (seasonal influenza)	Injection	IP and OP	Partial capture
CBER PRISM	Tripedia	Injection	IP and OP	Partial capture
CBER PRISM	Twinrix	Injection	Predominantly OP	Near complete capture
CBER PRISM	Typhim Vi	Injection	Predominantly OP	Near complete capture
CBER PRISM	Tyvac	Injection	Predominantly OP	Near complete capture
CBER PRISM	Vaqta	Injection	Predominantly OP	Near complete capture
CBER PRISM	Varivax	Injection	Predominantly OP	Near complete capture
CBER PRISM	Vivotif	Oral	Predominantly OP	Near complete capture
CBER PRISM	YF-Vax	Injection	Predominantly OP	Near complete capture
CBER PRISM	Zostavax	Injection	Predominantly OP	Near complete capture

V. APPENDIX B. CANDIDATE HEALTH OUTCOMES OF INTEREST

Acute disseminated encephalomyelitis
Acute hemolytic transfusion reaction (AHTR)
Acute myocardial Infarction
Acute Kidney Injury
Agranulocytosis
ALS - Amyotrophic lateral sclerosis
Anaphylaxis and anaphylactoid reactions
Angioedema
Aplastic Anemia
Atrial Fibrillation
Bell's palsy
Bleeding
Blind
Brachial neuritis
Bronchospasm
Cerebrovascular Accident (CVA)/Transient Ischemic Attack (TIA)
Ischemic stroke
Chronic Renal Failure
Colitis, ischemic
Congenital anomalies
Congestive Heart Failure
Deaf
Depression
Disseminated intravascular coagulation
Dyslipidemias
Endotoxic shock, confirmed or suspected
Erythema Multiforme Major, including SJS and TENS
GI Bleeding
GI Ulcer Hospitalization
Guillain-Barre syndrome
Hemorrhagic stroke
Hemolysis
Hemolytic anemia
Henoch-Schonlein purpura
Hip Fracture
Histoplasmosis
Hospitalization
Hyperglycemia
Hypertensive crisis
Hypoglycemia
Idiopathic thrombocytopenic purpura
Inflammatory Bowel Disease
Intussusception
Juvenile rheumatoid arthritis
Kawasaki disease
Lactic acidosis
Liver Failure
Lymphoma
Mania/Bipolar
Medical device removal/revision
Myocarditis
Narcolepsy
Neuroleptic malignant syndrome
Optic neuritits
Pancreatitis
Pancytopenia
Pericarditis
PML - Progressive multifocal leukoencephalopathy
Pneumonia
Post-transfusion allergic reaction
Premature Delivery
Pulmonary Fibrosis
Pulmonary hypertension
Respiratory Failure
Rhabdomyolysis
Rheumatoid arthritis
Schizophrenia
Seizures, afebrile
Seizures, febrile
Sepsis
Serotonin syndrome
Severe Acute Liver Injury
Spontaneous abortion
Stillbirth
Sudden Death
Suicide
Systemic lupus erythematosis
Tendonopathies
Thrombotic thrombocytopenic pupura (TTP)
Tics
Torsade de Pointes
Transfusion-related acute lung injury (TRALI)
Transverse myelitis
Tuberculosis
Type 1 diabetes
Uveitis
Valvulopathy
Venous Thromboembolism
Ventricular fibrillation

VI. APPENDIX C. STRUCTURED CONVERSATIONS WITH DATA PARTNERS

Structured conversations were held with each Data Partner in May, 2012. In advance of the call, we distributed questions related to capture of infused therapies, capture of claims for Medicare-eligible members, capture of claims for members with secondary sources of coverage, the potential for ad hoc updates to the MSDD, and access to inpatient data streams. Below we list the questions posed and a summary of the responses received.

1. Infusion Therapies

Question:
IV therapies can be administered in a variety of outpatient settings. To what extent do your source data include administrations in:

- physician offices
- outpatient clinics
- private infusion clinics
- long-term care settings
- other?

Response summary:
The general consensus is that all infused therapy claims that are submitted to insurance, regardless of setting, will be included in the data. Unpaid, denied, or reconciled claims are not always included, and the price of the procedure may influence whether the claim is submitted individually or bundled with other services. There is some question as to whether exposures in long-term care settings are captured reliably. Claims are filed but the format and content of those claims is unknown. Exploratory work is needed to understand which billing codes are used in which settings.

Question:
IV therapies may also be administered in inpatient settings. Under what circumstances will specific inpatient administrations be reflected in your data?

Response summary:
The main issue is whether claims for inpatient administrations are submitted as service-level claims or encounter-level claims (bundled). In encounter-level claims it is not possible to identify specific inpatient administrations. Health plan contracts with hospital providers may require that service-level detail be submitted and, in such cases, inpatient administrations will be captured. Revenue center codes may yield some insight into infused therapies, but will not identify specific products.

Question:
A variety of therapies are administered via IV infusion. To what extent do your source data accurately reflect administrations of:

- Drugs (chemotherapy, anti-infectives, etc.)
- Blood products

- RBC transfusion
- Platelet administrations
- IVIG
- Biologics (e.g., coagulation factor VIIa)

Response summary:
If the therapy is paid for specifically or submitted in a detailed claim then it will be captured. The cost of the therapy may influence whether a detailed claim is submitted. Expensive products often require a detailed claim, but less expensive products may be bundled with other services and ambiguously captured. Many partners are confident that chemotherapy will be captured, but there is uncertainty with non-chemotherapy drugs. We anticipate that Mini-Sentinel will acquire more detailed knowledge through protocol-based studies where the source record can verify the capture of specific therapies. Only one partner is confident that blood products will appear, but notes that revenue center codes may be used. Most other partners do not expect blood products to appear.

Question:
If you have IV therapies and infusions in your source data, what form do these take in terms of ability to load into the current MS-CDM? Dispensings? Procedures? Other?

Response summary:
J-codes, NDC, and HCPCS codes are all possibilities for coding of data. One data partner reviewed the summary table output based on specific J-codes and concluded that the CDM does not capture all exposures, probably because homegrown codes are used.

Question:
Are there available data streams for infused therapies that are not currently included in the MSCDM?

Response summary:
There is potential for data streams from facility claims, EMRs, EPIC, specialty pharmacy claims, and external pharmacy claims.

2. Medicare-Eligible Beneficiaries

Questions:
For your members 65 years and older, do you capture all inpatient and ambulatory encounters, diagnoses, and procedures, and their outpatient drug dispensings?

If there are different sets of members 65 years and older, are different enrollment/membership categories associated with incomplete capture of medical care (eg, plans that do not cover outpatient medications; Medigap plans that only provide supplemental coverage)? Please describe.

If you have enrollment/membership categories that systematically do not capture all medical or drug coverage (as described above), can you identify members aged 65 and older for whom you have complete capture and those that you do not?

Response summary:
Data partners vary in their approaches to including Medicare beneficiaries in the CDM. In general, most data partners with Medicare Advantage plans include Medicare beneficiaries in the CDM. Data partners who offer Medigap (supplemental) plans only do not include Medicare beneficiaries because primary claims will not be captured. Coordination of benefit issues arise with individuals who are still working.

3. Beneficiaries with Multiple Sources of Coverage

Questions:
Members not eligible for Medicare may also have multiple sources of insurance coverage. We'd like to know more about your understanding about completeness of medical utilization capture for these members, and the extent that you can identify members for whom you expect complete capture of medical and drug use.

Are different enrollment/membership categories associated with incomplete capture of medical care (eg, plans that do not cover outpatient medications; individual has primary coverage through another source)? Please describe.

If you have enrollment/membership categories that systematically do not capture all medical or drug coverage (as described above), can you identify those members for whom you have complete capture and those that you do not?

Response Summary:
Most partners believe the number of members with dual coverage to be small, so the impact is relatively small. In general, claims will be captured as long as the partner is the primary insurer. Some, but not all, data partners exclude members with secondary coverage. The assignment of primary vs. secondary insurer may be made after the coordination of benefits process is complete and the assignment can change over time. For that reason, one data partner noted that it is unclear whether a "primary insurer" flag would be informative.

4. Ad Hoc Updates to the MSDD

Questions:
What is the minimum turn-around time for a partial, ad hoc update (ETL of data for specific cohort of exposed individuals and comparators)? For a full ad hoc update? This assumes the current MS-CDM structure, but may require keeping the partial or ad hoc update separate from your scheduled ETL database.

What are the key determinants of feasibility?

We expect that the recency of data will vary by data stream. For example, outpatient pharmacy data will be more recent than inpatient claims or death data. Is this a reasonable assumption?

Response Summary:
For many data partners, the time necessary for an ad hoc update ranges from 2 to 6 weeks, although some partners estimated much longer turn-around times. (Note: The estimated turn-around time does not include data quality checking.) For some data partners, the usefulness of ad hoc updates is limited by how often the source data is updated. For example, if the source data are updated only every quarter, then an ad hoc update would not necessarily contain new data, even though it could technically be completed in 2 weeks. For some data partners, it may be possible to modify the ETL process to draw upon daily or weekly claims, but data stability would be a major issue.

5. Inpatient Data Streams

Questions:
Accessing inpatient data streams remains an area of interest. Are inpatient data streams available?

Response summary:
Several data partners expressed interest in exploring new data sources and researching new opportunities. Few data partners have direct access to inpatient data streams.

Does your organization have an i2b2 installation?

Response summary:
Only one data partner mentions directly having an i2b2 installation.