

VALIDITY OF ADMINISTRATIVE AND CLAIMS DATA FOR THE IDENTIFICATION OF CASES OF ANAPHYLAXIS IN THE MINI-SENTINEL DISTRIBUTED DATABASE

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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 healthcare 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.

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I. EXECUTIVE SUMMARY

A. OVERVIEW OF PROJECT

In May 2008, the U.S. Food and Drug Administration (FDA) launched the Sentinel Initiative, a long-term program designed to create a national electronic monitoring system for medical product safety (the Sentinel System).¹⁻² The Mini-Sentinel pilot is a collaborative effort between the FDA and a consortium of institutions, led by Harvard Pilgrim Healthcare Institute, to develop the scientific operations needed for the eventual Sentinel System. Since accurate and timely identification of health outcomes is an essential component of active safety surveillance, Mini-Sentinel convened a workgroup to establish a process for development and validation of an algorithm to identify cases of anaphylaxis using health plan administrative and claims data.

The algorithm development and validation process consisted of six parts: 1) development of an electronic claims-based algorithm to identify patients with anaphylaxis from medical claims; 2) formulation of a clinical definition for anaphylaxis for use with medical records data; 3) development of a method for the Data Partners to sample, retrieve, and de-identify medical records of a sample of patients who have been identified by the algorithm formulated in Step 1; 4) creation of a structured data abstraction form to enable collection of information relevant to the determination of anaphylaxis from medical records and abstraction by a trained abstractor; 5) adjudication of anaphylaxis cases based on physician review of the completed data abstraction forms; and 6) determination of the positive predictive value of the constructed algorithm.

B. SUMMARY OF FINDINGS

An algorithm which included diagnostic and procedure codes was developed with the goal of improving the positive predictive value (PPV) from previously published results. Data Partners provided charts with a median of 18 pages (range 1 to 604 pages). Adjudicators were asked to make a judgment on whether the case met the clinical definition of anaphylaxis. Of the 122 potential cases, adjudicators determined that 77 cases were anaphylaxis. Overall the PPV was 62.6% (95% confidence interval (95% CI), 53.4% to 71.2%). Using specific combinations of codes used in the original algorithm, we developed a modified algorithm with a higher PPV (75.0%) than the original algorithm but only 66% of confirmed cases would be identified using the modified algorithm (51 of 77 total confirmed cases). Among those cases which did not meet the clinical criteria for anaphylaxis, there were 16 cases for which clinician adjudicators agreed that the patients experienced severe allergic reactions, requiring emergent treatment. If the anaphylaxis cases and severe allergic reaction cases were combined, the PPV of the algorithm for identifying anaphylaxis or severe allergic reactions was 76.2% (95% CI, 67.7%-83.5%). Key decision points included: (1) balance of optimizing the positive predictive value (PPV) of the anaphylaxis algorithm while taking into account that anaphylaxis is potentially under-diagnosed; and (2) whether to include chart abstractions or have physicians review the medical records directly due to the short length of most records and the complexity of data being abstracted.

C. RECOMMENDATION FOR VALIDATION APPROACH AND SUGGESTION FOR FUTURE INVESTIGATIVE EFFORTS

While the PPV of the evaluated algorithm (63%) was higher than estimates reported in prior published studies, the PPV of the algorithm developed in this study remains low. Investigators using this algorithm

should be cognizant of the fact that it may misidentify as anaphylaxis a certain number of cases of severe allergic reaction, but that if used for purposes of drug surveillance, this may be acceptable. We evaluated the PPV in the overall population enrolled in eight health plans. For people exposed to a given drug or biologic and for a given post-exposure time period, PPVs of the algorithm (or specific criteria within the algorithm) may differ from our findings; therefore, further validation of the anaphylaxis algorithm may be warranted for specific study purposes.

II. BACKGROUND

The *Summary Report of the Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium* defines anaphylaxis as “a serious allergic reaction that is rapid in onset and may cause death.”⁴ Incidence rates reported in studies in U.S. populations vary greatly, ranging from approximately 10 to > 30 per 100,000 person-years.⁵⁻⁷ Discrepancies may be related to differences in the study populations, study design/case ascertainment methods, or the definition and criteria used to determine cases.

Published studies have reported that approximately 11 to 17% of cases of anaphylaxis were attributed to administration of a medication, immunotherapy, or a diagnostic agent.^{5,7} While the risk of anaphylaxis is not well-known for most medications, evaluation of spontaneous reports has led to black box warnings for a number of medications (e.g. omalizumab, aprotinin, paclitaxel), as well as withdrawal of zomepirac sodium.⁸

Few published studies have evaluated the validity of health plan administrative and claims data to identify anaphylaxis (**Table 1**).^{5-6,9} These studies are summarized in the *Mini-Sentinel Systematic Evaluation of Health Outcome of Interest Definitions for Studies Using Administrative Data: Anaphylaxis Report* (http://www.mini-sentinel.org/work_products/HealthOutcomes/Mini-Sentinel-HOI-Evidence-Review-Anaphylaxis-Report.pdf). In this report there were two studies which evaluated the validity of health plan administrative data to identify anaphylaxis^{5,9} and an additional study was published after the search results for the Mini-Sentinel report were completed.⁶

Bohlke et al. identified potential cases of anaphylaxis occurring between 1991 and 1997 in a population of children and adolescents enrolled in Group Health Cooperative, a health maintenance organization in Washington state.⁵ Investigators reviewed the medical charts of all potential cases identified using diagnosis codes specific for anaphylaxis (e.g. ICD-9-CM 995.0, other anaphylactic shock; ICD-9-CM 995.6, anaphylactic shock caused by adverse food reaction) and a sample of cases identified with other nonspecific codes (e.g. ICD-9-CM, 995.3, allergy unspecified). Administrative and claims data from hospitalizations, emergency department visits, and ambulatory encounters were assessed. The code with the highest positive predictive value was ICD-9-CM 995.0, with 55% of potential cases confirmed to be a probable or possible case of anaphylaxis. The positive predictive values for nonspecific codes were much lower; for example, the positive predictive value for ICD-9-CM 995.3 (allergy unspecified) was 1%.

Johannes et al. evaluated the incidence of allergic reactions after exposure to anti-bacterial agents among members enrolled in a large U.S. health plan from July 2000 to June 2004.⁹ For patients with an emergency department or hospitalization claim for anaphylaxis (ICD-9-CM 995.0), medical record review was conducted. Sixteen of 28 patients (57%) with this code were confirmed to have anaphylaxis.

Iribarren et al. evaluated the validity of ICD-9- CM code 995.0 among a cohort of patients diagnosed with asthma and a comparison group of patients without asthma enrolled in Kaiser Permanente Northern California between 1996 and 2006.⁶ Administrative and claims data from hospitalizations, emergency department visits, and ambulatory encounters were assessed. Medical record review was conducted and cases were confirmed based upon the *Summary Report of the Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium*.⁴ Of the 109 potential cases reviewed, 57 (52%) were confirmed as likely/probable cases.

In summary, the epidemiology of drug-induced anaphylaxis is not well-described. Given the severity of the condition, drug-induced anaphylaxis is a major public health concern. Limited data have been published on the validity of health plan administrative and claims data for the identification of anaphylaxis. A validated method of identifying anaphylaxis using administrative data would facilitate evaluation of the risk of anaphylaxis associated with medications and biologics of interest for the post-market surveillance of medical products within the Mini-Sentinel (MS) program.

III. METHODS

A. OVERVIEW OF DESIGN FOR THE ANAPHYLAXIS VALIDATION

The Mini-Sentinel Anaphylaxis Validation project was a collaboration between the FDA, the Mini-Sentinel Operations Center (MSOC), and selected Academic and Data Partners. Five Mini-Sentinel Data Partners participated in this project: (1) HealthCore, Inc.; (2) Humana; (3) three member health plans within the Kaiser Permanente Center for Effectiveness and Safety Research; (4) two member health plans within the HMO Research Network; and (5) Vanderbilt University.

The validation process consisted of six parts: 1) development of an **electronic claims-based algorithm** to identify patients with anaphylaxis; 2) identification of a **clinical definition for anaphylaxis** for use with medical records data; 3) development of a method for the Data Partners to **sample, retrieve, and de-identify medical records** from a sample of patients identified by the algorithm formulated in Step 1; 4) creation of a structured data abstraction form to enable collection of information relevant to the determination of anaphylaxis from medical records and **abstraction** by a trained abstractor; 5) physician **adjudication** to determine whether potential cases were anaphylaxis by reviewing the data abstraction forms and using the clinical definition; and 6) determination of the **positive predictive value** of the constructed algorithm.

In collaboration with the Mini-Sentinel Operations Center and the FDA, the workgroup reviewed the *Mini-Sentinel Systematic Evaluation of Health Outcome of Interest Definitions for Studies Using Administrative Data: Anaphylaxis Report* (http://www.mini-sentinel.org/work_products/HealthOutcomes/Mini-Sentinel-HOI-Evidence-Review-Anaphylaxis-Report.pdf) and other research studies that have employed administrative data for identification of anaphylaxis cases. Clinical guidelines for the diagnosis of anaphylaxis were also reviewed.⁴ The workgroup used this information to develop a case definition of anaphylaxis. The case definition included elements of the clinical history, including presenting symptoms, time interval between exposure (if known) and onset of symptoms, and treatment received.⁴ Unlike acute myocardial infarction, for which laboratory and electrocardiographic data facilitate the diagnosis, the diagnosis of anaphylaxis is a clinical diagnosis based primarily on history and physical exam findings. In addition, acute serious cases are expected to be treated in a number of different medical practice settings

requiring sampling and review of medical records from inpatient, emergency department, and outpatient encounters. This information was used to guide the development and validation of an algorithm to identify potential cases of anaphylaxis.

B. DEVELOPMENT OF AN ELECTRONIC CLAIMS-BASED ANAPHYLAXIS

1. B1. Determination of Possible Codes of Interest

The goal of this project was to develop and validate an algorithm to identify cases of anaphylaxis using administrative health plan data. The algorithm described below (section B.2) was selected to include sets of codes that will have a high positive predictive value, while also addressing the concern that the condition is underdiagnosed.

a) B.1.a. Codes for ‘Other Anaphylactic Shock (ICD-9-CM 995.0) and Anaphylactic Shock due to Serum (ICD-9-CM 999.4)

Two ICD-9-CM diagnosis codes specifically indicating anaphylaxis include 995.0 (other anaphylactic shock) and 999.4 (anaphylactic shock due to serum). The validity of code 995.0 has been evaluated in a few studies (Table 1).^{5-6,9} These studies report positive predictive value estimates ranging from approximately 52 to 57% for this specific code. Bohlke *et al.* reported a positive predictive value of 0% for code 999.4; however, only 10 potential cases were evaluated. We were unable to identify any other studies that validated this code. The study by Bohlke *et al.* also reported that 71% of confirmed cases of anaphylaxis (overall) were seen in the emergency department (ED) or urgent care and 19% were seen in an outpatient clinic; 11% resulted in hospitalization. Iribarren *et al.* reported that 21% of encounters identified with 995.0 were actually determined to be cases for which the patient had a history of anaphylaxis, rather than an acute event on the specific encounter date.

Thus, the results of these studies suggest that further qualifiers should be included with codes 995.0 and 999.4 to result in a higher positive predictive value for these two codes. The algorithm described below selects all inpatient and ED encounters with ICD-9-CM codes 995.0 and 999.4. The algorithm selects outpatient encounters with these codes only if additional qualifiers (symptoms or treatment codes) are also present during the encounter. For outpatient encounters, patients with an encounter in the prior 30 days that documents an anaphylaxis code (995.0, 999.4) are excluded. The rationale for this differentiation includes: 1) studies evaluating the validity of codes for other disease states have generally indicated higher positive predictive values for inpatient and ED codes than outpatient/ambulatory codes, 2) the study by Iribarren *et al.* suggests that a substantial proportion of encounters may be follow-up visits (history of) for the diagnosis, which would occur in an outpatient setting, 3) a preliminary query of data from MS data partners indicated that the number of outpatient/ambulatory encounters with code 995.0 documented is approximately 7-fold higher than the number of ED encounters (or inpatient encounters), which is contrary to the distribution of encounters with confirmed cases reported by Bohlke *et al.*

Qualifiers for outpatient visits include the following diagnoses or treatments: bronchospasm, stridor, hypotension, epinephrine, injection of diphenhydramine, or CPR. These diagnoses and treatments were selected based upon the definition described in the *Summary Report of the second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium*,⁴ as well as

descriptions of the symptoms and treatment patterns described in the studies by Bohlke *et al.* and Iribarren *et al.*

Our rationale for excluding patients with an anaphylaxis code within 30 days prior to the index date from the primary analysis is to reduce the likelihood of identifying patients who are presenting for follow up of a prior anaphylaxis event.

b) B.1.b. Additional Nonspecific Codes (ICD-9- CM 995.3, 995.2 and E930-E949) Potentially Used to Identify Cases of Anaphylaxis

ICD-9-CM diagnosis codes 995.3 (allergy unspecified), 995.2 (other and unspecified adverse effect of drug, medicinal and biological substance [due] to correct medicinal substance properly administered) and E930-E949 (drugs, medicinal and biological substances causing adverse effects in therapeutic use) are included in the algorithm described below to potentially identify undocumented cases of anaphylaxis. Bohlke *et al.* reported a positive predictive value of 1% for code 995.3. Given the very low positive predictive value for this code and the results of a preliminary query of data from MS data partners, which indicated that the number of encounters with 995.3 is approximately 20-fold higher than the number of encounters with code 995.0 (other anaphylactic shock), additional qualifiers have been added for this code. No published studies have used codes 995.2 or E930-E949 to identify anaphylaxis. In addition, the results of a preliminary query of data from MS data partners indicated that the number of encounters with 995.2 is approximately 10-fold higher than the number of encounters with code 995.0.

Thus, at least two additional criteria are included in the algorithm for encounters with ICD-9-CM codes 995.3, 995.2, and E930-E949 for patients to be selected as a potential case. Specifically, encounters should include both: 1) evidence of an allergic component (codes for bronchospasm, stridor, or injection of diphenhydramine) and 2) treatments or symptoms more specific to a serious allergic reaction/anaphylaxis (hypotension, epinephrine, or cardiopulmonary resuscitation [CPR]). Only ED and inpatient encounters were included to reduce the number of false positives.

2. B2. Final Algorithm for Identification of Cases of Anaphylaxis

Based upon information from published studies, preliminary data from the data partners, and clinical guidelines, the algorithm evaluated included the following diagnosis and procedure codes.

Encounter with ICD-9-CM code

Criterion A: (995.0 [other anaphylactic shock] or 999.4 [anaphylactic shock due to serum]) inpatient or emergency department encounter

OR

Criterion B: (995.0 [other anaphylactic shock] or 999.4 [anaphylactic shock due to serum]) outpatient encounter **PLUS** a code for one of the following symptoms/procedures/treatments:

- i. bronchospasm (519.11) or
- ii. stridor (786.1) or

- iii. hypotension (458.9) or
- iv. epinephrine (J0170 or J0171) OR
- v. injection of diphenhydramine (J1200) or
- vi. CPR (92950 or 99.60)

OR

Criterion C: (995.3 [allergy unspecified] or 995.2 [other unspecified adverse effect of drug] or E930-E949 [drugs, medicinal and biological substances causing adverse effects in therapeutic use]) inpatient or emergency department encounter

- vii. **PLUS** a code for one of the following symptoms/procedures/treatments:
 - 1. bronchospasm (519.11) or
 - 2. stridor (786.1) or
 - 3. injection of diphenhydramine (J1200)
- viii. **and ALSO** a code for one of the following symptoms/procedures/treatments
 - 1. hypotension (458.9) or
 - 2. epinephrine (J0170 or J0171) or
 - 3. CPR (92950 or 99.60)

For inpatient and ED codes: all patients who met inclusion criteria were sampled.

For outpatient encounters: All patients who met inclusion criteria, excluding patients with an encounter in the prior 30 days that documented an anaphylaxis code (995.0 or 999.4) were sampled.

Table 2 shows the definitions for the included codes.

C. CLINICAL DEFINITION OF ANAPHYLAXIS

The clinical definition of anaphylaxis for confirmation of cases is taken from the *Summary Report of the Second Symposium on the Definition and Management of Anaphylaxis from the Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network Symposium*.⁴ The criteria includes three different clinical situations in which anaphylaxis should be considered; these include a combination of skin, respiratory, blood pressure, and GI symptoms. (**Table 3**) This definition was selected because it is the most widely used criteria, developed from two symposiums. The clinical definition stipulates that symptoms may occur up to “several hours” after the exposure. Michelle Conroy, MD, Assistant Professor of Medicine at the University of Massachusetts Medical School, and a board-certified allergist-immunologist, consulted with us on the time frame for onset of anaphylaxis. Based on this input, we allowed a maximum of 8 hours from the known exposure for our clinical definition.

D. SAMPLING, RETRIEVAL, AND DE-IDENTIFICATION OF MEDICAL RECORDS

1. D1. Identification and sampling of potential cases

The goal of this Mini-Sentinel activity was to validate the diagnostic codes used to identify likely anaphylaxis cases across all Data Partners. We estimated that a simple random sample of 100 would allow determination of the positive predictive value of the diagnostic coding algorithm for anaphylaxis with a

95% confidence interval of ± 0.8 , assuming a positive predictive value of 80%. Thus, we determined that 100 charts would be sufficient to obtain an overall assessment of the PPV, although this limited sample would be insufficient to evaluate the sensitivity of the PPV across a full range of scenarios relating to Data Partners and patient characteristics. Since the purpose of this workgroup was to develop an algorithm that could identify cases of anaphylaxis within observational cohorts with minimal misclassification, we chose to focus on the positive predictive value. We felt that optimizing this parameter would allow researchers sufficient confidence in the coding-based algorithm for future use.

Based on the algorithm described above (Section B.2), the Operations Center developed a SAS program, tested it with two Data Partners for accuracy, and then distributed it to all Data Partners participating in the project. In order to identify a random sample of anaphylaxis cases and the hospitals in which they received care, participating Data Partners executed the SAS program to query their own locally maintained administrative and claims data. Mini-Sentinel uses a distributed data approach in which Data Partners maintain physical and operational control over electronic data in their existing environments. Data Partners execute standardized programs provided by the Operations Center and then share the output of these programs, typically in summary form, with the Operations Center. Data Partners transform their data into the Mini-Sentinel Common Data Model (MSCDM) format in order to standardize administrative and clinical information across Data Partners prior to running the SAS programs. To obtain approximately 100 cases for eventual adjudication, efforts were made to identify 150 cases distributed across all participating Data Partners, with all but one participating Data Partner pursuing an equal number of cases (one Data Partner sampled 60 cases, rather than 30, to better ensure that a minimum of 30 charts would be obtained).

The following Data Partners of the Mini-Sentinel Network participated: Vanderbilt; HealthCore, Inc.; Humana; three member health plans within the Kaiser Permanente Center for Effectiveness and Safety Research (Kaiser Permanente Colorado, Kaiser Hawaii, Kaiser Permanente Northwest); and two member health plans in the HMO Research Network (HealthPartners, Harvard Pilgrim Health Care). Eligible patients had at least 30 days of continuous enrollment in their respective health plan prior to the encounter date identified with a code or codes suggestive of anaphylaxis (see section B.2) recorded between January 1, 2009 and December 31, 2010. There were no restrictions on age, sex, other diagnoses, or other patient characteristics.

Together, the Mini-Sentinel Distributed Database encompasses demographic data, medical diagnoses (recorded using ICD-9-CM diagnostic codes), medical procedures, and prescription claims maintained by each Mini-Sentinel Data Partner locally behind established firewalls. In 2010, the Office for Human Research Protections at the Department of Health and Human Services determined that the Common Rule does not apply to activities conducted under the Sentinel Initiative.¹⁰ Therefore, the Mini-Sentinel Anaphylaxis Workgroup and institutions participating as Data Partners did not need to obtain review of this study by their respective Institutional Review Boards or seek to obtain waivers of authorization under the Health Insurance Portability and Accountability Act (HIPAA).

2. D2. Retrieval and redaction of medical records

The Operations Center was primarily responsible for establishing protocols for ensuring the privacy of data and for explaining the status of this data collection activity as public health surveillance. The Operations Center provided each Data Partner with a privacy packet prepared by the Mini-Sentinel

Privacy Panel (**Appendix A**). This packet included: (1) the Mini-Sentinel Privacy Panel White Paper describing data privacy issues in Mini-Sentinel; (2) a letter from the Department of Health and Human Services' Office for Human Research Protections (OHRP) to the FDA stating that the regulations OHRP administers do not apply to the Sentinel Initiative (OHRP oversees all IRBs); (3) a letter from the FDA to the Mini-Sentinel Principal Investigators stating that Mini-Sentinel is a Sentinel Initiative activity); and (4) a letter from FDA which indicated that the anaphylaxis validation project is a Sentinel/Mini-Sentinel project. The privacy packet described the legal basis for determining that the work of the Mini-Sentinel pilot constituted a public health activity not under the purview of the IRB. Data Partners were asked to disseminate this information to their IRBs and Privacy Boards as well as any other relevant entities. The Operations Center also provided an instructional flowchart and customizable letter template to provider sites in the activity protocol. The letter (addressed to each provider site from specific Data Partners) explained the purpose of the project and explained what was being requested. Letters also explained that the request was being carried out on behalf of Mini-Sentinel and the FDA (**Appendix A**). The flowchart outlined the array of possible scenarios for chart retrieval and detailed the steps for chart redaction and data transmission (**Appendix A**).

Data Partners asked source data holders (e.g., individual medical records departments) for access to the medical records for sampled patients for the identified medical encounter. Source data holders either sent the medical records to vendors commissioned to extract, copy, and redact the requested information, or allowed Data Partners direct access to records for extraction, copying, and redaction. Redaction of individually identifiable information was performed in accordance with HIPAA's "minimum necessary standard."

The Mini-Sentinel Operations Center worked with the Data Partners to obtain redacted photocopies or printouts of relevant portions of the medical records. A Data Partner medical record extraction checklist was developed (**Appendix B**); the Data Partners completed and transmitted the checklist to the Mini-Sentinel Operations Center for each sampled potential case, along with the redacted portions of the medical records.

Components of the medical record that were requested from the Data Partners for validation purposes from a hospitalization of interest included: physician notes (including history and physical notes, discharge summaries, progress notes, consult notes, death notes), all orders, nursing medication administration record, all available information on vital signs (heart rates, blood pressures, temperature, respiration rate, pulse oxygenation level), allergy list, and transfer note (if applicable). From an emergency department visit of interest, it included: all emergency room notes, all EMT/ambulance notes, all orders, nursing medication administration record, and all available information on vital signs (heart rates, blood pressures, temperature, respiration rate, and pulse oxygenation level). From an outpatient visit of interest, the requested chart sections included all clinician notes from the visit date, all EMT/ambulance notes (if applicable), all vitals from the visit date, all orders from the visit date, medication administration record if any medications administered in clinic, allergy list, and outpatient allergist notes from 30 days after the visit date. (**Table 4**)

Designated staff at each Data Partner or vendors contracted by the Data Partners completed chart redactions internally. Redaction of individually identifiable information was performed in accordance with HIPAA's provisions for a 'limited dataset,' which is an alternative to using fully de-identified information. Under HIPAA, creation of a limited dataset requires removal of 16 direct identifiers, but

allows for the inclusion of dates, geographic location (not as specific as street address), and any other code or characteristic not explicitly excluded.¹¹ Redaction was completed before the chart components were transferred to the Operations Center. Each Data Partner assigned a new, de-identified ID unique to each redacted chart prior to transferring extracted data, and maintained a crosswalk between the newly assigned IDs and the original (also de-identified) IDs.

Data Partners were provided with credentials to login to the Mini-Sentinel Secure Portal for transferring, managing, or retrieving chart components. Security was managed within the folder structure of the site; the Secure Portal contains private folders accessible only to specified members within each Data Partner site and authorized Operations Center staff, as well as common folders defined for all users. Data Partners electronically uploaded redacted charts to their site-specific private folders. The Operations Center verified that all charts were redacted thoroughly and then moved all files to a separate private folder, allowing the lead team access to the data. While the Operations Center is allowed to receive un-redacted medical chart data based on Mini-Sentinel's status as a public health surveillance activity,¹⁰ every effort was made to de-identify the data prior to its transmission to the Operations Center.

Redacted chart data were sent to the Mini-Sentinel Operations Center via the Mini-Sentinel Secure Portal. Through this website, the redacted medical records were made available to the study team for centralized abstraction and adjudication.

E. DATA ABSTRACTION

The workgroup developed and tested a medical record abstraction form to be used in validating anaphylaxis (**Appendix C**). A list of elements of the medical record considered essential to the validation and adjudication process was developed by the workgroup. For each case, the availability of each of the essential elements of the medical record was recorded. For example, blood pressure was considered an essential element, and the presence or absence of blood pressure measurements was recorded during abstraction. The form was developed for easy use by abstractors who were not clinical experts in anaphylaxis. The Co-PI (KW) performed a pilot test of the form for content in a sample of 10 medical records (separate from the identified cases within the random sample).

Abstraction was performed by two trained abstractors. The study team trained the data abstractors to enter abstracted information onto a paper form and provided the abstractors with an instruction manual. During the piloting of the data abstraction forms, the abstractors and Co-PI (KW) both performed abstractions on the first 10 selected patients from the data partners. The physician adjudicators reviewed the first 10 completed data abstraction forms to ensure that the data gathered in the abstraction form was accurate and comprehensive.

F. ADJUDICATION

The workgroup developed an adjudication form for clinical experts to evaluate data from the medical record abstraction and determined whether or not the case could be confirmed as anaphylaxis (**Appendix D**). The adjudication form included judgments about whether anaphylaxis occurred. The workgroup convened three clinicians with expertise relevant to anaphylaxis (two emergency department physicians and one allergist) to adjudicate all abstractions. The clinician experts were trained in the adjudication process. Two clinician experts independently reviewed abstraction materials to make a judgment about whether anaphylaxis occurred, using the clinical definition of anaphylaxis as a gold standard. In cases where the two clinician experts did not agree regarding whether anaphylaxis

occurred, the experts discussed and came to consensus. If they could not agree after discussion, a third clinician expert reviewed the abstraction materials and made a judgment. Inter-rater reliability was calculated using Cohen's kappa statistic.¹² The kappa scores between adjudicator pairs were found to be 0.52, 0.58, and 0.66, which indicates moderate agreement.

Because there was little information in previous publications about cases found not to be anaphylaxis, the workgroup attempted to identify clinical diagnoses for cases identified by the algorithm but not judged to meet clinical criteria. Two physicians, including a workgroup co-lead investigator (KW) and one allergist, reviewed each of these cases independently and developed a taxonomy for their diagnoses.

G. DATA ANALYSIS

For our primary analysis, we determined the positive predictive value of the anaphylaxis electronic claims-based algorithm for confirmed definite events. For secondary analyses, we also calculated PPVs by patient age group (0 -10 years, 11-19 years, 20-64 years, \geq 65 years), gender, Data Partner, and each 'set' of criteria outlined in the algorithm (A,B,C; section B.2). We evaluated the PPVs of individual ICD-9-CM codes and combinations of codes used in the algorithm. We also calculated PPVs overall and for each set of criteria using a composite outcome of anaphylaxis/serious allergic reaction (confirmed definite events of either anaphylaxis or serious allergic reaction). Exact binomial confidence intervals were calculated (<http://statpages.org/confint.html>).

In the overall Data Partner population, we also determined the frequency of encounters and patients with each code (diagnosis and procedure) outlined in the algorithm (overall and according to encounter type) to assess the relative use of the codes across Data Partners during the study period.

IV. RESULTS

A. CASE RETRIEVAL RESULTS

1. A1. Percent of charts obtained

One of the 150 potential cases of anaphylaxis randomly selected was found to not meet criteria for selection (did not meet criteria A, B, or C) after the Data Partner updated their MS Common Data Model. Of the 149 potential cases meeting criteria, medical records for 131 (88%) were available for review (**Figure 1**). Reasons that medical record information was not obtained included: provider refusal and /or required patient consent (n=4), facility has no record of patient (n=1), facility has no record of patient in time frame (n=2), facility actively refuses to participate and/or has additional HIPAA/IRB requirements (n=1), no response from facility after multiple attempts to contact them (n=4), there was insufficient information (n=2), and unknown (n=4). Retrieval rates across the Data Partners ranged from 77% to 100% of potential cases identified from health plan data. Of the 131 medical records located, 9 were determined to have inadequate information to confirm whether or not a case was anaphylaxis. In most cases, this was because the medical record did not contain adequate information. For example, one record was an outpatient follow up visit only to an emergency department visit for anaphylaxis. The medical chart for the emergency department visit was not available. All subsequent analyses for the calculation of PPVs included the 122 patients for whom medical records with adequate information to

assess case status were available for review. The distributions of gender, age, and specific criteria categories were generally similar for potential cases with a chart review and potential cases for whom the charts were unavailable. (**Table 5**) Of the patients for whom charts were abstracted, 63% were female and 62% were ages 20 to 64 years.

2. A2. Available chart components

Table 6 shows the chart components requested and obtained for inpatient charts, ED charts, and outpatient charts. The availability of requested components was generally high (> 80%) for inpatient and ED charts, and somewhat lower for outpatient charts (< 80%) for all requested components.

3. A3. Chart size

There was a large amount of variability in the average amount of chart materials forwarded by the Data Partners (measured by number of pages). Larger amounts of chart materials led to slower abstraction and likely required a greater expenditure of resources on the part of the Data Partner (time and resources spent copying and redacting). The median number of pages was 18; the range was 1-604 pages, and there were 34 medical records which were less than 10 pages.

B. ABSTRACTION AND ADJUDICATION RESULTS

Of the 122 potential cases, adjudicators determined that 77 cases were anaphylaxis. Overall, the PPV was 63.1% (95% confidence interval, 53.9%-71.7%). PPVs ranged from 48.1% to 78.9% across the Data Partners (**Table 7**). While the PPV for criterion C (PPV=45.8%) was lower than the PPVs for criteria A and B (PPVs of 69.0% and 65.2%, respectively), confidence intervals were wide and overlapped. The distribution of criteria met varied across Data Partners; no patients at Data Partner 2 (which had the highest PPV) met criterion C, while more than one-quarter of the patients at Data Partners 1 and 5 (which had the lowest PPVs) met criterion C (n= 10 and 7, respectively).

Patients may have met more than one set of criteria on the encounter date of interest. The PPVs were slightly lower for cases that met only one criterion: 68.0% (95% CI, 56.2%-78.3%) for criterion A, 60.0% (95% CI, 36.1%-80.9%) for criterion B, and 38.9% (95% CI, 17.3%-64.3%) for criterion C. Of the 77 confirmed cases of anaphylaxis, only 7 cases (9%) met criterion C only.

Table 8 shows the PPVs for individual ICD-9-CM codes and combinations of codes used in the algorithm. While several combinations of codes had high PPVs, few cases were identified based upon these combinations. For example, while the PPVs for patients with both an anaphylaxis code (ICD-9-CM 995.0) and a code for hypotension (ICD-9-CM 458.9) were 100% for each encounter type (inpatient, emergency department, or ambulatory), only 6 cases had this combination of codes documented in the administrative data.

Table 9 shows potential alternative algorithms to identify cases of anaphylaxis using administrative data. The PPV of an algorithm including criteria A and B only (and not C) was 67.3% (95% CI 57.4% - 76.2%); while excluding criterion C would only increase the overall PPV slightly, the algorithm would be less complex and would include 91% of confirmed cases. Alternatively, if we used an algorithm that included only codes/combinations of codes with positive predictive values > 70% (see Table 8), we could

create an algorithm with a PPV of 75.0% (95% CI, 63.0% – 84.7%); however, only 66% of confirmed cases would be identified using this algorithm (51 of 77 total confirmed cases).

If the 9 cases for which there was inadequate information in the medical chart were included in the analyses (as unconfirmed cases), the resulting overall PPV is 58.8% (95% CI, 49.9%-67.3%; 77 confirmed cases from a total of 131 cases for which a chart was located), with PPVs ranging from 46.4% to 69.2% across Data Partners.

Of the 45 potential cases not confirmed to be anaphylaxis, 16 (36%) were determined to be a serious allergic reaction. The physician reviewers defined a severe allergic reaction as an allergic reaction which is highly likely to evolve into anaphylaxis if untreated. For the composite outcome of anaphylaxis/serious allergic reaction, the PPV was 76.2% (95% CI, 67.7%-83.5%; 93 confirmed definite events of either anaphylaxis or serious allergic reaction from a total of 122 cases with adequate information in the medical chart). For this composite outcome, the PPVs were 83.3% (95% CI, 73.6%-90.6%), 78.3% (95% CI, 56.3%-92.5%), and 54.2% (95% CI, 32.8%-74.5%) for criteria A, B, and C, respectively. The PPV of the algorithm including criteria A and B only (and not C) was 81.7% (95% CI 73.0% - 88.6%); 85 of 104 confirmed definite events of either anaphylaxis or serious allergic reaction (91%) were identified using this criteria.

C. RELATIVE USE OF PROCEDURE CODES ACROSS DATA PARTNERS

The frequency of the specific diagnosis (ICD-9-CM) and procedure (ICD-9 , CPT, HCPCS) codes used in the algorithm varied greatly across Data Partners, with the largest variability observed with the procedure codes of interest (data not shown). The prevalence of patients identified with codes for CPR ranged from 22 to 276 per 100,000 across Data Partners for CPT code 92950 and ranged from 7 to 81 per 100,000 across Data Partners for ICD-9 code 99.60. The prevalence of patients identified with codes for an injection of adrenalin/epinephrine (HCPCS code J0170) ranged from 16 to 646 per 100,000 across Data Partners, and the prevalence of patients identified with codes for an injection of diphenhydramine (HCPCS code J1200) ranged from 121 to 1602 per 100,000 members.

V. SUMMARY AND CONCLUSIONS

The PPV of the evaluated algorithm (63%) was higher than estimates reported in prior published studies, which have reported PPV estimates ranging from 52 to 57% for ICD-9-CM code 995.0 (other anaphylactic shock).^{5-6,9} In the present study, we found that the criteria that included codes specifically indicating anaphylaxis (ICD-9-CM codes 995.0 and 994.0) had higher PPVs than criterion with codes indicating allergy or adverse effects of drugs (criterion C), even when qualifiers (additional diagnosis or procedure codes indicating symptoms or treatment of anaphylaxis) were included in such criterion. However, even if we omitted the criterion including codes for allergy and adverse effects of drugs from the overall algorithm, the resulting PPV estimate would be < 70%.

Strengths of our study include evaluating the validity of administrative and claims codes from 8 large health plans located in different geographic regions of the U.S. In addition, the diagnoses originated from data of both HMO-owned and community medical care settings. Thus, our findings are likely generalizable to other U.S. health plans and data systems. We also were able to identify medical

records for the great majority of patients (88%) selected for chart abstraction and were able to obtain adequate information to make a decision regarding anaphylaxis in 82% of cases.

Limitations of this study include the fact that, in some cases, insufficient information was found in the medical record to adequately determine the case status. Misclassification bias may have resulted if study subjects were not categorized correctly with regards to outcome. However, the likelihood of misclassification was minimized by employing two adjudicators to confirm events, with a third to adjudicate cases in instances of disagreement. The patients in these analyses are all drawn from databases of insured persons, potentially limiting the generalizability of our results to other populations. We found considerable variability in the use of the procedure codes in the overall Data Partner populations, with more than a 10-fold difference in the prevalence of patients identified with procedure codes for CPR, injection of epinephrine, and injection of diphenhydramine across Data Partners; whether this represents a true difference in the treatments administered or variability in coding practices is uncertain. In addition, the sample size did not allow adequate evaluation of the PPV for specific codes; a larger sample size would have allowed for more precise estimates (narrower confidence intervals for PPVs). Lastly, we only evaluated patients with codes suggestive of anaphylaxis or allergy and did not include patients known not to have anaphylaxis or allergy conditions; thus, we could not evaluate the sensitivity and specificity of the algorithm.

LESSONS LEARNED

The workgroup identified several lessons which we believe are important for future Mini-Sentinel endeavors. These include:

1. Working with a diagnosis for which the existing literature reflects a low PPV presents several challenges. Addressing these prior to the start of the validation effort may help keep the project efficient and on schedule.

In the case of anaphylaxis, the workgroup recognized that frequent underdiagnosis and failure to bill for anaphylaxis contributes to missed cases of anaphylaxis, both in clinical practice and in administrative databases. The workgroup assessed whether it would be possible to enhance sensitivity of the algorithm by including procedure codes as well as a broader array of ICD9-CM codes. Given our expectation of a low PPV even in the setting of more restricted algorithm, the prospect of broadening the algorithm prompted extended discussion among workgroup members. We asked whether optimizing sensitivity but designing an algorithm with a very low PPV would yield a useful product and whether it would lend insights of sufficient value. This was an important process to work through but contributed to delays at the start of the validation effort and led to downstream delays due to changes in available staff. We recommend that future validation efforts build on the experience of our workgroup and that decisions on balancing sensitivity vs. optimal PPV should ideally be addressed prior to the start of the project.

2. Validating a health outcome whose diagnosis is made largely on clinical criteria including physical exam findings or patient-reported symptoms can be challenging both for abstractors and adjudicators.

A careful and skilled medical record abstraction is essential to accurate adjudication. This was particularly the case for anaphylaxis since it is not a health outcome easily confirmed through lab

studies, imaging or other test reports. Upon recognizing that 43% of the medical records obtained were shorter than the 15 page abstraction form, the workgroup considered discontinuing abstraction and allowing adjudicators to simply review medical records. Advantages to this approach would have included avoiding the intermediate steps of training abstractors and of performing abstraction. It would also allow expert adjudicators direct access to each medical record. Due to the presence of some inpatient records with several hundred pages, the workgroup decided to pursue the original approach of abstraction followed by adjudication, but also provided each adjudicator with access to the complete deidentified chart, to review at their discretion. In some cases, adjudicators chose to review the medical record along with the abstraction form to obtain a more complete picture of the clinical situation.

Information on possible diagnoses other than anaphylaxis (for example, a suspected pulmonary embolus in a patient with respiratory distress) was deemed essential for accurate adjudication. It was a challenge to develop appropriate training techniques so that abstractors could adequately gather information on alternate possible diagnoses without expending excess effort on chart review. There was little information in the literature about cases in prior studies which were found not to be anaphylaxis (and which contributed to the published low PPVs). Without this information, it was difficult to anticipate the factors which contribute to a low PPV, to include these factors in the abstraction form, and to train abstractors to search for them. After abstraction of an initial set of charts, this challenge was identified and abstractors received additional training to ensure capture of information about other possible diagnoses.

Given the importance of a thorough abstraction, incomplete charts limited abstraction and adjudication in some cases.

3. Routine periodic updates to databases carried out by Data Partners can lead to slight changes when data are updated or refreshed. Future workgroups should understand that there is a window of opportunity to check the quality of data before the data are refreshed by data partners.

In our study, workplans were run initially to identify the sample of patients for chart abstraction and adjudication and also several months later to identify individual level data for secondary analyses after medical records were abstracted and adjudicated. In the second workplan, one of the cases identified in the initial workplan as being an inpatient visit was identified as an outpatient visit, and no longer met criteria for a potential case of anaphylaxis. The information from that case, which we abstracted and adjudicated, was excluded from final analysis. While this is a minor problem, it highlights the need to quality check data early on and immediately address any concerns before the Data Partners refresh their data.

4. There are several steps in the validation process where upstream delays can have a magnified effect on downstream deadlines. Anticipating and planning around this reality may help future validation efforts meet their deadlines more consistently.

Early delays stemming from the need to clarify goals around sensitivity and PPV pushed back start times for hired abstractors and adjudicators, missing windows in which dedicated time was set aside for this project and leading to overlap with times of lower availability (summer vacation). In order to move forward more quickly, abstractor training was then initiated once 5 medical records were uploaded onto the secure portal. Abstractors then independently reviewed 10 records, but had to wait until an

additional 10 records were available before receiving their follow-up training (described above under Lessons Learned, #2).

5. A balance between completing the current project in a timely manner and investigating questions important to the larger Mini-sentinel initiative was necessary.

The workgroup chose, at times, to pursue questions which arose because such questions were important to the larger Mini-sentinel initiative, while not central to the immediate project. For example, the workgroup delayed the final report to further understand cases which were not anaphylaxis but which were severe allergic reactions. If the project had been a freestanding study, rather than part of a group of studies, the workgroup might have decided to delay assessing severe allergic reactions for a future grant or paper. While this exploration was not central to the main objective of validating an anaphylaxis algorithm, the workgroup considered this information important for future workgroups studying the association between specific drugs and severe allergic reactions.

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Table 1. Summary of studies evaluating the positive predictive values of algorithms used to identify cases of anaphylaxis using health plan data (edited from Mini-Sentinel Systematic Evaluation of Health Outcome of Interest Definitions for Studies Using Administrative Data to Identify Cases of Anaphylaxis, Schneider et al.)

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm	Validation/Adjudication Procedure	Validation Statistics
Bohlke et al. ⁴	<p>Group Health Cooperative data, 1991–1997.</p> <p>The study population consisted of the 229,422 children and adolescents under the age of 18 years.</p>	anaphylaxis from all causes	<p>Codes specific to anaphylaxis: 995.0, 995.6, 999.4, 995.4</p> <p>Codes not specific to anaphylaxis: 989.5, 708.0, 708.9, 995.1, 695.1</p>	Validation was performed via chart review.	<p>PPVs for codes specific to anaphylaxis:</p> <p>995.0 (anaphylactic shock) = 55.4%.</p> <p>995.6 (anaphylactic shock caused by adverse food reaction) = 9.8%.</p> <p>999.4 (anaphylactic shock caused by serum) = 0%.</p> <p>995.4 (shock caused by anesthesia) = 0%.</p> <p>PPVs for codes not specific to anaphylaxis:</p> <p>989.5 (toxic effect of venom) = 4.7%.</p> <p>708.0 (allergic urticaria) = 5.6%.</p> <p>708.9 (urticaria unspecified) = 0%.</p> <p>995.1 (angioneurotic edema) = 7.4%.</p> <p>995.3 (allergy, unspecified) = 1.3%.</p> <p>695.1 (erythema multiforme) = 0%</p>

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm	Validation/Adjudication Procedure	Validation Statistics
Johannes et al. ⁸	Ingenix Research Data Mart. The study population comprised patients receiving at least 1 dispensing of moxifloxacin, ciprofloxacin, levofloxacin, gatifloxacin, phenoxymethylpenicillin potassium, or a combined group of first-, second-, and third-generation cephalosporins, 2000 to 2004.	serious allergic reactions after fluoroquinolone, cephalosporin, and phenoxymethylpenicillin potassium exposure, emergency department (ED) or hospitalization (inpatient)	Inpatient or ED visit bearing ICD-9 diagnosis codes of 995.0, 995.2, 995.3, a CPT code of 92950 for cardiopulmonary resuscitation, or an HCPCS code for adrenaline injection (J7640).	Medical record review was conducted.	PPV for 995.0 (anaphylactic shock) = 57.1% (16 of 28). PPVs for 995.3 (allergy, unspecified) and 995.2 (unspecified adverse effect of drug) were not reported. PPV for CPT 92950 (cardiopulmonary resuscitation) and HCPCS J7640 (adrenaline injection) combined = 2.9% (1 of 35).
Iribarren, Carlos et al. ⁵ <i>ADDED TO TABLE, not in original report</i>	Kaiser Permanente Northern California members with asthma and cohort without asthma. 1996-2006.	anaphylactic shock	Hospitalizations, ambulatory visits and ED visits w ICD9 codes 995.6 (anaphylactic shock caused by adverse food reaction), 999.4 (anaphylactic shock caused by serum) and 995.0 (other anaphylactic shock). Also looked at incidence of other selected allergy-related dx: 708.0 (allergic urticaria); 989.5 (anaphylaxis after stings) and	Medical record review was conducted. Confirmation of cases based on criteria developed at Second NIAID/Food Allergy and Anaphylaxis Network symposium.	Only validated 995.0 which they describe as: "extreme nonfood allergy causing respiratory distress and vascular collapse." Likely/probably: PPV 52% Likely/probably + history of: PPV 72%

Citation	Study Population and Time Period	Description of Outcome Studied	Algorithm	Validation/Adjudication Procedure	Validation Statistics
			995.1 (angioneurotic edema.)		

Table 2. Codes included in the algorithm to identify cases of anaphylaxis using health plan administrative and claims data

ICD-9-CM diagnosis codes:

995.0 = Other anaphylactic shock
 995.2 = Other and unspecified adverse effect of drug, medicinal and biological substance (due) to correct medicinal substance properly administered;
 995.3 = Allergy unspecified
 999.4 = Anaphylactic shock due to serum
 E930-E949 = Drugs, medicinal and biological substances causing adverse effects in therapeutic use
 519.11 = Acute bronchospasm
 786.1 = Stridor
 458.9 = Hypotension unspecified

2009 HCPCS codes:

J0170 = Injection, adrenalin, epinephrine, up to 1 ml ampule
 J0171 = Injection, adrenalin, epinephrine, 0.1 mg
 J1200 = Injection, diphenhydramine hcl, up to 50 mg

CPT code:

92950 = CPR

ICD-9-CM procedure code:

99.60 = CPR

Table 3. Clinical Criteria for Diagnosing Anaphylaxis⁴

Anaphylaxis is highly likely when any of the following 3 criteria are fulfilled:

-
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:
 - a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)

 2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue uvula)
 - b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - c. Reduced BP or associated symptoms (eg, hypotonia [collapse] syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)

 3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
 - a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
 - b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP
-

Abbreviations: PEF, Peak expiratory flow; BP, blood pressure.

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

Table 4. Requested Chart Elements List and Decision Tree for Data Partners

Type of medical records and minimal data elements needed for Anaphylaxis Validation

The medical chart, stripped of all direct identifiers,¹ should include all paper² and electronic information corresponding to the designated inpatient, emergency department, or outpatient encounter (from date of admission to date of discharge for inpatient stays):

Emergency Room

1. All Emergency room notes
2. All EMT/ambulance notes
3. All orders
4. Nursing medication administration record
5. All available information on vital signs (heart rates, blood pressures, temperature, respiration rate, pulse oxygenation level)
6. Allergy list
7. Transfer note (if applicable)

Inpatient

*If patient came in through ED, in addition to items below, please also include everything in ED list above.

1. Physician notes (including history and physical notes, discharge summaries, progress notes, consult notes, death notes)
2. All orders
3. Nursing medication administration record
4. All available information on vital signs (heart rates, blood pressures, temperature, respiration rate, pulse oxygenation level)
5. Allergy list
6. Transfer note (if applicable)

Outpatient

1. All clinician notes from the visit date
2. All EMT/ambulance notes (if applicable)
3. All vitals from the visit date
4. All orders from the visit date
5. Medication administration record if any medications administered in clinic
6. Allergy list
7. Outpatient allergist notes from 30 days after the visit date

¹ The information provided will not include any data elements that directly identify individuals, but may include ages over 89 years, dates of service, or geographic subdivisions smaller than states or 3-digit zip codes. All of the 16 direct identifiers that would be excluded in the creation of a limited dataset, as enumerated in HIPAA, will be redacted. These include: Names, Telephone #s, Fax #s, Email addresses, SSNs, MRNs, Health plan beneficiary #s, Account #s, Certificate/License #s, Vehicle Identifiers and serial #s, including license plate #s, Device identifiers and serial #s, Web URLs, IP address #s (Internet), Biometric identifiers, including fingerprints and voiceprints, Full-face photographic images and any comparable images, and Any other unique identifying number, characteristic, or code, unless otherwise permitted by Privacy Rule for re-identification.

² If the paper chart for the designated hospital stay includes copies of information from prior medical records, these should be included.

ANAPHYLAXIS CHART ELEMENTS DECISION TREE

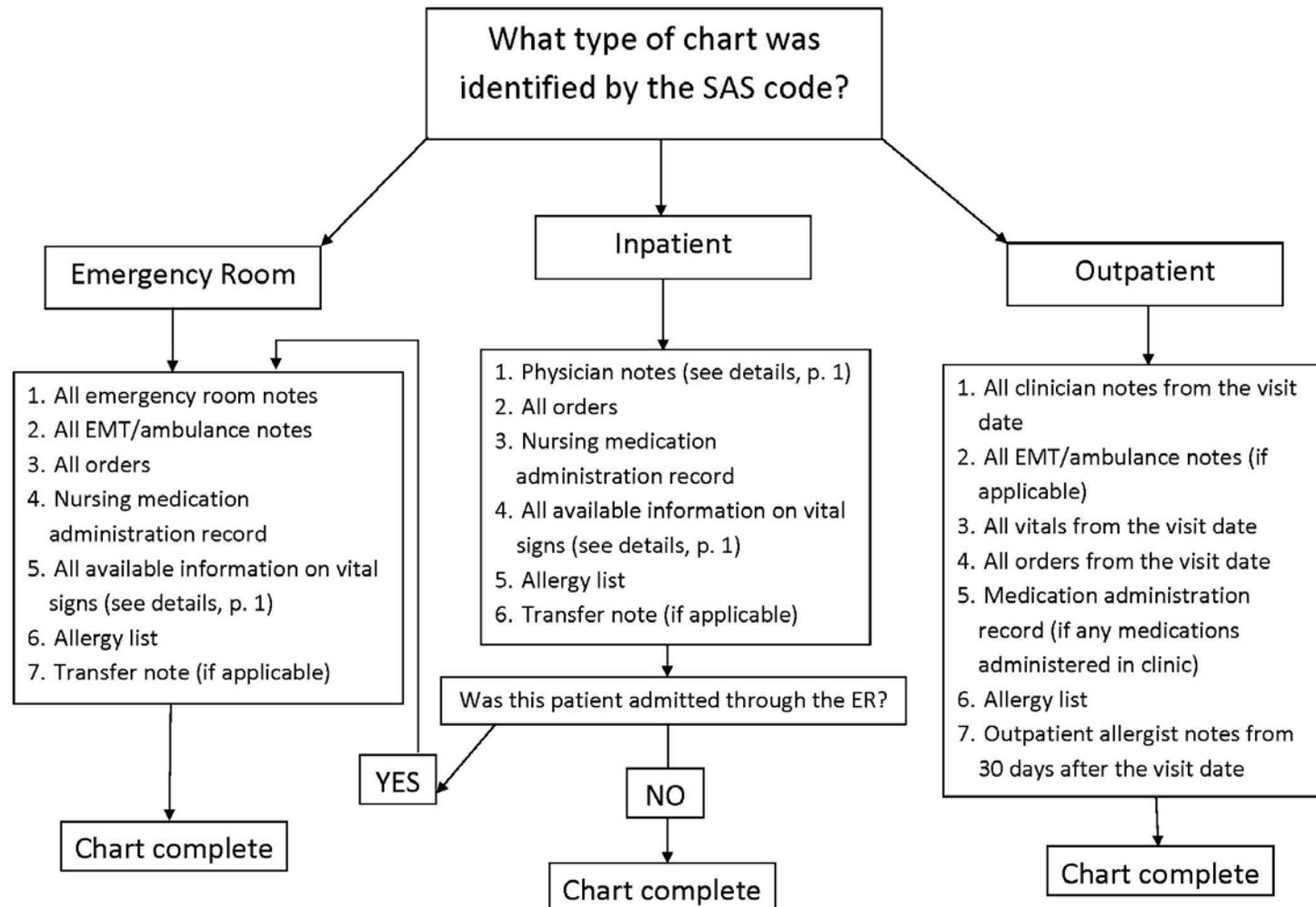


Table 5. Characteristics of eligible patients sampled for chart review

	Chart obtained, adequate information extracted N (%)	Chart obtained, inadequate information extracted N (%)	Chart not obtained N (%)	Total N (%)
Total patients	122	9	18	149
Patient Sex				
Female	77 (63.1)	4 (44.4)	13 (72.2)	94 (63.1)
Male	45 (36.9)	5 (55.6)	5 (27.8)	55 (36.9)
Patient Age (years)				
0 to 10	13 (10.7)	0	0	13 (8.7)
11 to 19	17 (13.9)	0	1 (5.6)	18 (12.1)
20 to 64	75 (61.5)	8 (88.9%)	13 (72.2)	96 (64.4)
≥ 65	17 (13.9)	1 (11.1)	4 (22.2)	22 (14.8)
Data Partner				
1	27 (22.1)	3 (33.3)	0	30 (20.1)
2	19 (15.6)	4 (44.4)	7 (38.9)	30 (20.1)
3	26 (21.3)	0 (0.0)	3 (16.7)	29 (19.5)
4	23 (18.8)	1 (11.1)	6 (33.3)	30 (20.1)
5	27 (22.1)	1 (11.1)	2 (11.1)	30 (20.1)
Specific Criteria*				
Criterion A	84 (68.9)	5 (55.6)	11 (61.1)	100 (67.1)
Criterion B	23 (18.9)	2 (22.2)	5 (27.8)	30 (20.1)
Criterion C	24 (19.7)	2 (22.2)	3 (16.7)	29 (19.5)
Encounter Type*				
Emergency Department	75 (61.5)	3 (33.3)	11 (61.1)	89 (59.7)
Inpatient	31 (25.4)	4 (44.4)	2 (11.1)	37 (24.8)
Outpatient	23 (18.9)	2 (22.2)	5 (27.8)	30 (20.1)

* Total of rows sum to more than the total charts, since patients may have met more than one set of criteria on the encounter date of interest

Table 6. Available components among charts requested*

	Total	
Emergency Department		
Total Potential Cases	95	72.0%
Records with the requested components		
ER notes	91	95.8%
EMT notes	13	13.7%
All orders	85	89.5%
Nursing medication administration record	82	86.3%
All vital signs	91	95.8%
Allergy list	86	90.5%
Transfer note	15	15.8%
Inpatient		
Total Potential Cases	42	31.8%
Records with the requested components		
Physician notes	38	90.5%
All orders	34	81.0%
Nursing medication administration record	35	83.3%
All vital signs	38	90.5%
Allergy list	37	88.1%
Transfer note	1	2.4%
Copies of all items in ER list	29	69.0%
Outpatient		
Total Potential Cases	36	27.3%
Records with the requested components		
Clinician notes	28	77.8%
EMT notes	0	0.0%
All vital signs	27	75.0%
All orders	28	77.8%
Medication administration record	24	66.7%
Allergy list	27	75.0%
Outpatient allergist notes >30 days	11	30.6%

* Includes information on all charts received (including those 9 patients with inadequate information to determine case status and 1 patient found not to meet criteria for selection). Total encounter types sum to more than the total patients sampled, since Data Partners may have requested more than one medical record for the encounter date of interest. In some instances, Data Partners provided the medical charts from encounter dates or encounter types other than those requested by the workgroup.

Table 7. Validation of diagnosis and procedure codes in health plan administrative databases for identification of anaphylaxis

	Number of charts reviewed	Number of cases confirmed	Positive predictive value (95% confidence interval)
Total patients	122	77	63.1% (53.9% - 71.7%)
Patient Gender			
Female	77	53	68.8% (57.3% - 78.9%)
Male	45	24	53.3% (37.9% - 68.3%)
Patient Age (years)			
0 to 10	13	8	61.5% (31.9% - 86.1%)
11 to 19	17	10	58.8% (32.9% - 81.6%)
20 to 64	75	48	64.0% (52.1% - 74.8%)
> 65	17	11	64.7% (38.3% - 85.8%)
Data Partner			
1	27	16	59.3% (38.8% - 77.6%)
2	19	15	78.9% (54.4% - 94.0%)
3	26	18	69.2% (48.2% - 85.7%)
4	23	15	65.2% (42.7% - 83.6%)
5	27	13	48.1% (28.7% - 68.1%)
Specific Criteria*			
Criterion A	84	58	69.0% (58.0% - 78.7%)
Criterion B	23	15	65.2% (42.7% - 83.6%)
Criterion C	24	11	45.8% (25.6% - 67.2%)
Encounter Type*			
Emergency Department	75	45	60.0% (48.0% - 71.2%)
Inpatient	31	24	77.4% (58.9% - 90.4%)
Outpatient	23	15	65.2% (42.7% - 83.6%)

* Total of rows sum to more than the total charts reviewed, since patients may have met more than one set of criteria on the encounter date of interest

Table 8. Validation of diagnosis and procedure codes in health plan administrative databases among patients meeting criteria for identification of anaphylaxis*

	Number of charts reviewed	Number of cases confirmed	Positive predictive value (95% confidence interval)
Criterion A			
Other anaphylactic shock (ICD-9-CM 995.0)			
Overall	82	57	69.5% (58.4% - 79.2%)
Inpatient			
All inpatient encounters	30	23	76.7% (57.7% - 90.1%)
<i>Concurrent treatment/symptom codes</i>			
Injection adrenalin/epinephrine (HCPCS J0170, J0171)	2	2	100.0% (15.8% - 100.0%)
Injection diphenhydramine (HCPCS J1200)	1	2	50.0% (1.3% - 98.7%)
Cardiopulmonary Resuscitation (ICD-9 99.60, CPT 92950)	1	1	100.0% (2.5% - 100.0%)
Hypotension (ICD-9-CM 458.9)	4	4	100.0% (39.8% - 100.0%)
Emergency Department			
All emergency department encounters	56	38	67.9% (54.0% - 79.7%)
<i>Concurrent treatment/symptom codes</i>			
Injection adrenalin/epinephrine (HCPCS J0170, J0171)	16	12	75.0% (47.6% - 92.7%)
Injection diphenhydramine (HCPCS J1200)	19	13	68.4% (43.5% - 87.4%)
Cardiopulmonary Resuscitation (ICD-9 99.60, CPT 92950)	1	1	100.0% (2.5% - 100.0%)
Hypotension (ICD-9-CM 458.9)	1	1	100.0% (2.5% - 100.0%)
More than 1 encounter type (inpatient, emergency department, ambulatory) with a code for anaphylaxis	17	15	88.2% (63.6% - 98.5%)
Anaphylactic shock due to serum (ICD-9-CM 999.4)			
Overall	3	2	66.7% (9.4% - 99.2%)
Inpatient	1	1	100.0% (2.5% - 100.0%)
Emergency Department	2	1	50.0% (1.3% - 98.7%)
Criterion B			
Other anaphylactic shock (ICD-9-CM 995.0)			
Overall (ambulatory)	21	14	66.7% (43.0% - 85.4%)
<i>Concurrent treatment/symptom codes</i>			

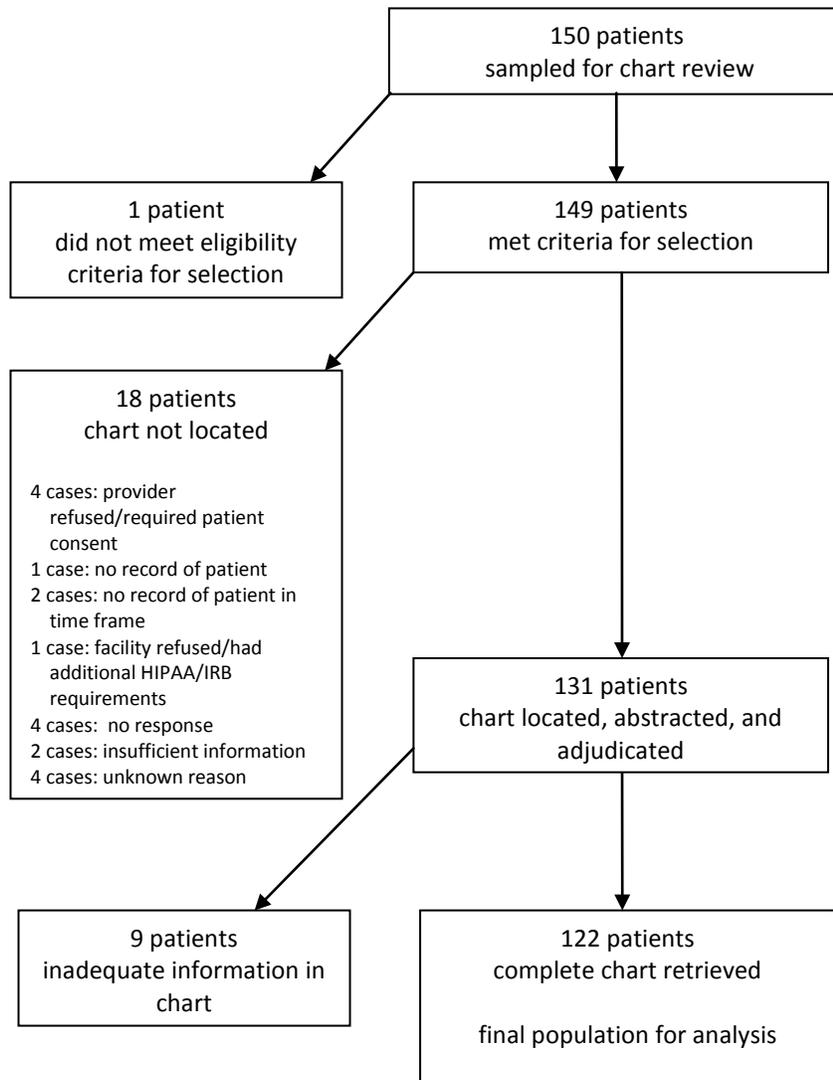
	Number of charts reviewed	Number of cases confirmed	Positive predictive value (95% confidence interval)
Injection adrenalin/epinephrine (HCPCS J0170, J0171)	14	10	71.4% (41.9% - 91.6%)
Injection diphenhydramine (HCPCS J1200)	9	6	66.7% (29.9% - 92.5%)
Cardiopulmonary resuscitation (ICD-9 99.60, CPT 92950)	1	1	100.0% (2.5% - 100.0%)
Hypotension (ICD-9-CM 458.9)	2	2	100.0% (15.8% - 100.0%)
Anaphylactic shock due to serum (ICD-9-CM 999.4)			
Overall (ambulatory)	2	1	50% (1.3% - 98.7%)
Criterion C			
Inpatient			
Drugs, medicinal and biological substances causing adverse effects in therapeutic use (ICD-9-CM E930-E949)	1	1	100.0% (2.5% - 100.0%)
Emergency Department			
Overall	23	10	43.5% (23.2% - 65.5%)
Other and unspecified adverse effect of drug (ICD-9-CM 995.2)	3	3	100.0% (29.2% - 100.0%)
Allergy unspecified (ICD-9-CM 995.3)	17	5	29.4% (10.3% - 56.0%)
Drugs, medicinal and biological substances causing adverse effects in therapeutic use (ICD-9-CM E930-E949)	4	2	50.0% (6.8% - 93.2%)

* Codes documented in ≥ 2 cases in the overall population sampled for chart review were evaluated. All patients meeting criterion C met the criterion based upon codes for injection of adrenalin/epinephrine and injection of diphenhydramine (no other codes of interest were documented); thus, combinations of codes were not evaluated.

Table 9. Potential algorithms for identification of anaphylaxis using health plan administrative databases

	Number of charts reviewed	Number of cases confirmed	Positive predictive value (95% confidence interval)
Evaluated algorithm (patients meeting criteria A, B, or C)	122	77	63.1% (53.9% - 71.7%)
Patients meeting criteria A or B	104	70	67.3% (57.4% - 76.2%)
<p>Patients with codes/combinations of codes with positive predictive values > 70% (see Table 8):</p> <p>1) ≥ 1 inpatient anaphylaxis code (ICD-9-CM 995.0 or 999.4) Or</p> <p>2) ≥ 1 emergency department or ambulatory other anaphylaxis code (ICD-9-CM 995.0)] PLUS [a concurrent treatment/symptom code for injection adrenalin/epinephrine (HCPCS J0170, J0171) or cardiopulmonary resuscitation (ICD-9 99.60, CPT 92950) or hypotension (ICD-9-CM 458.9)] Or</p> <p>3) > 1 encounter type (inpatient, emergency department, ambulatory) with a code for anaphylaxis Or</p> <p>4) Patients meeting criterion C who were identified with code for unspecified adverse effect of drug (ICD-9-CM 995.2) only [not using codes for allergy unspecified (ICD-9-CM 995.3) or drugs, medicinal and biological substances causing adverse effects in therapeutic use (ICD-9-CM E930-E949)]</p>	68	51	75.0% (63.0% – 84.7%)

Figure 1. Chart Sampling and Retrieval



VIII. APPENDICES

A. APPENDIX A. PRIVACY PACKET BY THE MINI-SENTINEL PRIVACY PANEL

June 2011

Dear Mini-Sentinel Colleagues,

The Mini-Sentinel Privacy Packet has been amended to include documentation that clarifies that all Harvard Pilgrim Health Care, Inc. (HPHC) subcontractors that perform services for HPHC in fulfillment of contract number HHSF2232009100061 (the FDA Mini-Sentinel pilot) are subject to the same contractual requirements concerning the privacy and confidentiality of commercial confidential information and health care data, including but not limited to protected health information (PHI), as are subcontractors that are named as Collaborating Institutions. All subcontractors are likewise subject to the provisions of the Mini-Sentinel statement of Principles and Policies.

The following pages include (1) the original Privacy Packet materials dated July 19, 2010 and (2) the new materials dated June 30, 2011.

Please contact [Susan Forrow](#) with any questions.

The Mini-Sentinel Operations Center

July 19, 2010

Dear Mini-Sentinel Colleagues,

We are providing the attached White Paper and associated Exhibits to clarify that Mini-Sentinel's activities, conducted under contract with and under the authority of the Food and Drug Administration (FDA), are public health surveillance activities. Consequently, Mini-Sentinel activities do not come under the purview of Institutional Review Boards (IRBs) or Privacy Boards. We believe the attached documents will enable your institution to understand the reasoning behind this determination, as well as its implications. We expect these documents will also provide assurance, as we collectively undertake this important pilot, that Mini-Sentinel activities will be conducted with the utmost respect for the privacy of individual health information.

Please contact [Susan Forrow](#) with any questions regarding these materials.

The Mini-Sentinel Operations Center

Attachments:

- HIPAA and Common Rule Compliance in the Mini-Sentinel Pilot
- Exhibit 1: Letter from OHRP to FDA
- Exhibit 2: Letter from FDA to Rich Platt re. OHRP
- Exhibit 3: Letter from FDA to Rich Platt re. public health authority status

HIPAA and Common Rule Compliance in the Mini-Sentinel Pilot

*Authored by the Mini-Sentinel Privacy Panel:
Kristen Rosati, Barbara Evans and Deven McGraw¹*

Executive Summary

This paper addresses compliance under the Common Rule and the Health Insurance Portability and Accountability Act (HIPAA)² for data sources participating in Mini-Sentinel, a pilot project of the Food and Drug Administration's (FDA) Sentinel Initiative, mandated by Congress in the Food and Drug Administration Amendments Act of 2007. First, as explained below, the use of data for Mini-Sentinel is a public health activity, not research. The Director of the Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP) has determined that the Common Rule does not apply to activities conducted as part of the Sentinel Initiative Institutions participating as data sources therefore do not need to obtain review by their Institutional Review Boards (IRBs) to participate in Mini-Sentinel or to provide data for Mini-Sentinel purposes.

Second, HIPAA applies to most data sources participating in Mini-Sentinel. The access, use, and disclosure of protected health information (PHI) for purposes of Mini-Sentinel are public health activities that may be conducted without individual authorization. Moreover, data sources may rely on documentation from the FDA regarding the legal authority of the FDA and its contractors and subcontractors (including the Mini-Sentinel Coordinating Center and its Collaborating Institutions) that they are acting as public health authorities. While data sources must comply with HIPAA's minimum necessary standard in releasing PHI for Mini-Sentinel, data sources may rely on the determination by the FDA and its contractors and subcontractors regarding what constitutes the minimum amount of information necessary for the request.

This White Paper presently does not address data source compliance with the federal Part 2 regulations governing substance abuse treatment information, or compliance with state health information confidentiality laws. It will be updated in the future to discuss those compliance issues.

¹ This White Paper was produced by the Mini-Sentinel Privacy Panel as a general reference source and is not meant to provide legal advice to any person or entity that receives a copy of the work.

² Pub. L. No. 104-191, 110 Stat. 1936 (codified as amended at scattered sections of 18, 26, 29, 42 U.S.C.).

I. Introduction: Data Flow in the Mini-Sentinel Pilot

Consistent with its mission to protect and promote the public health, the FDA is embarking on the Sentinel Initiative to create an electronic system operating across different data environments – provider electronic health records, health plan claims databases, and other electronic health care data – to monitor medical products approved by the FDA. The Sentinel Initiative will strengthen FDA’s ability to monitor the performance of medical products after approval and will improve the FDA’s current medical product safety surveillance capabilities.

The creation of the Sentinel Initiative is required by the Food and Drug Administration Amendments Act of 2007 (FDAAA). Section 905 of this statute calls for HHS to develop methods to obtain access to disparate electronic health care data and to establish an active post-market risk identification and analysis system that links and analyzes healthcare data from multiple environments. The law sets a goal of access to data from 25 million patients by July 1, 2010, and 100 million patients by July 1, 2012. The law also requires FDA to work closely with partners from public, academic, and private entities.

Mini-Sentinel is a pilot project of the Sentinel Initiative intended to provide the foundational work necessary to inform and facilitate the development of a fully operational active surveillance system for monitoring the safety of FDA-regulated medical products (the Sentinel System). The Mini-Sentinel pilot is being conducted as a collaborative effort by a consortium that includes a variety of hospital systems, health plans, universities, and research institutes (called the Collaborating Institutions in this paper).³

³ The Collaborating Institutions include:

1. America’s Health Insurance Plans (AHIP)
2. Brigham and Women’s Hospital Division of General Medicine
3. Brigham and Women’s Hospital Division of Pharmacoepidemiology & Pharmacoeconomics
4. CIGNA Healthcare
5. Cincinnati Children’s Hospital Medical Center
6. Columbia University Department of Statistics
7. Critical Path Institute (C-Path)
8. Duke University School of Medicine
9. HealthCore, Inc.
10. HMO Research Network including: Group Health Research Institute (GHRI) at the University of Washington (UW); Harvard Pilgrim Health Care Institute (HPHCI); Health Partners Research Foundation; Henry Ford Health Systems; Lovelace Clinic Foundation; Marshfield Clinic Research Foundation; Meyers Primary Care Institute (Fallon)
11. Humana-Miami Health Services Research Center (HSRC)
12. Kaiser Permanente Center for Safety and Effectiveness Research (CESR) including: Northern California (KPNC); Southern California (KPSC); Colorado (KPCO); Northwest (KPNW); Georgia (KPSE); Hawaii (KPHI); Ohio (KPOhio); MidAtlantic (KPMidAtlantic)
13. Outcome Sciences, Inc. (Outcome)
14. Risk Sciences International (RSI)
15. Rutgers University Institute for Health
16. University of Alabama at Birmingham (UAB)
17. University of Illinois at Chicago (UIC)
18. University of Iowa, College of Public Health
19. University of Pennsylvania School of Medicine
20. Vanderbilt University School of Medicine

The objective of the Mini-Sentinel pilot is to inform and facilitate the development of the Sentinel System and carry out mandates delineated in FDAAA. Specifically, the Mini-Sentinel contract funds the development of a single Mini-Sentinel Coordinating Center with continuous access to electronic healthcare data systems, which will:

1. Provide a "laboratory" for developing and evaluating scientific methodologies that might later be used in a fully-operational Sentinel System;
2. Offer the FDA the opportunity to evaluate safety issues in existing electronic healthcare data systems; and
3. Learn more about some of the barriers and challenges, both internal and external, faced in creating a medical products safety surveillance system.

Representatives of the Mini-Sentinel Collaborating Institutions provide ongoing scientific, technical, methodologic, and governance expertise, as well as access to data, as needed to meet the requirements of the project. They participate in various capacities, including as data sources and as members of the Planning Board, the Safety Science Committee, the Cores (Data, Methods, and Protocol), and Working Groups for Task Orders and other activities.

No directly identifiable data will flow to the Mini-Sentinel Coordinating Center or to the FDA. Collaborating Institutions will maintain physical and operational control over the data. They will execute analysis programs distributed by the Coordinating Center, and provide the output of these programs to the Coordinating Center. Whenever possible, the output they share will contain only summary or aggregate information, such as counts of health plan members categorized by: 1) the presence or absence of a particular health condition; 2) exposure to a particular medication; 3) the presence or absence of a particular health outcome; and 4) age group. When person-level information is provided, it will be stripped of all directly identifiable data. For example, in order to confirm an adverse drug reaction, the Collaborating Institutions may provide clinical data about a particular individual, but this data will exclude any direct identifiers such as name and contact information.

21. Weill Cornell Medical College

The data flows for Mini-Sentinel are reflected in Figure 1 and Figure 2:

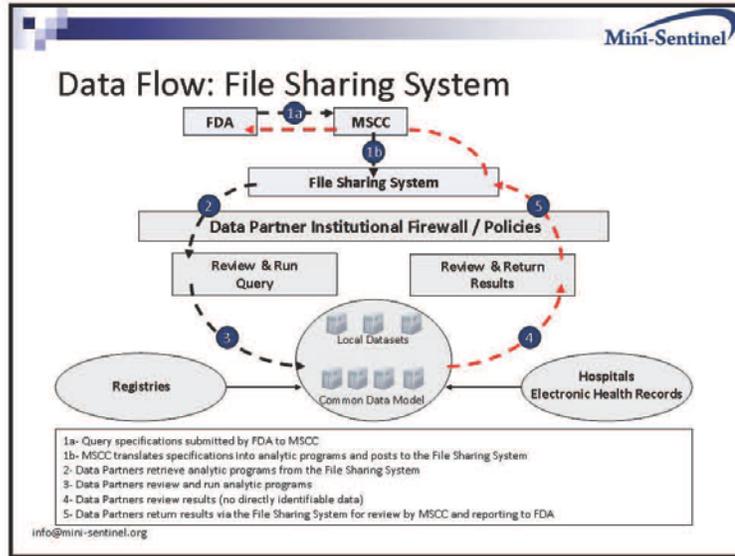


Figure 1

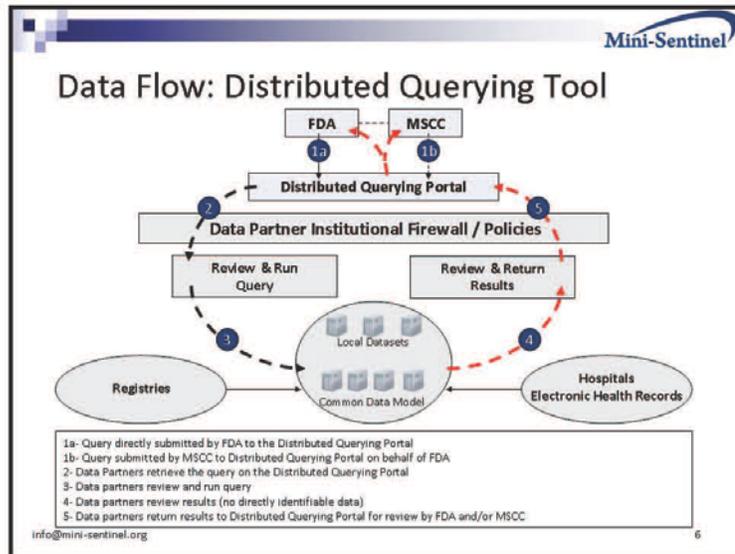


Figure 2

It is possible that some of the aggregate data flowing to the Coordinating Center will technically be “protected health information” (PHI) under HIPAA because the information reported may include dates of service or geographic codes (data elements that are listed as HIPAA “identifiers”), or because the information may represent “small cells” in which the diagnosis is sufficiently unique to be able to identify an individual if paired with other available information. Because data that is classified as PHI may flow to the Coordinating Center, we evaluate below whether this would comply with the HIPAA Privacy Rule.⁴

Moreover, it is possible that fully-identifiable PHI may flow from HIPAA covered entities to the Collaborating Institutions to confirm the validity of adverse event drug safety signals. For example, a Collaborating Institution might ask for portions of the medical record from a treating health care provider to determine if the drug in question was administered before or after the adverse clinical event occurred, or to determine whether other patient conditions may have resulted in the adverse clinical event observed. Another example involves state immunization registries: to evaluate the safety of immunizations, Collaborating Institutions may seek information from immunization registries regarding whether individuals have received certain immunizations. Because PHI may flow to the Collaborating Institutions, we evaluate below whether this would comply with the HIPAA Privacy Rule.⁵

This paper first addresses Common Rule compliance for any data source supplying information to the FDA, the Mini-Sentinel Coordinating Center, or the Collaborating Institutions, for the purpose of the Mini-Sentinel pilot.

II. Common Rule Compliance

The Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP) has concluded that activities related to the Sentinel Initiative are not covered by 45 CFR part 46 (the “Common Rule”). This means that cooperation in responding to Sentinel queries does not require review by an Institutional Review Board (IRB). On January 19, 2010, Jerry Menikoff, Director of the OHRP, wrote a letter to Rachel Behrman, then Acting Associate Director of Medical Policy, Center for Drug Evaluation and Research at the FDA, explaining that OHRP “has determined that the regulations this office administers (45 CFR part 46) do not apply to the activities that are included in the [FDA] Sentinel Initiative.” (See Exhibit 1.) Dr. Behrman then wrote on April 2, 2010, to Dr. Richard Platt at Harvard Pilgrim Health Care (the Mini-Sentinel’s prime contractor managing the Coordinating Center), providing Dr. Menikoff’s letter and concluding that the OHRP’s “assessment applies to the work being conducted by [Harvard Pilgrim Health Care] and its subcontractors under contract number HHSF2232009100061, as the purpose of this contract is to carry out Sentinel Initiative activities that are included in the [FDA] Sentinel Initiative.” (See Exhibit 2.) Thus, disclosure of information for Mini-Sentinel purposes is not subject to the Common Rule. This means that data sources providing information for Mini-Sentinel purposes are not required by federal regulation

⁴ 45 C.F.R. Part 160 and Part 164, Subpart E.

⁵ In this version of the White Paper we do not address compliance with state health information confidentiality laws, such as state laws governing permissible disclosures by their immunization registries. . . .

to obtain approval of their IRBs for participation in Mini-Sentinel, and are not required to obtain a determination from their IRBs that these activities are “exempt.”

III. HIPAA Compliance

A. Disclosures of Protected Health Information in Support of Mini-Sentinel Are for Public Health Activities under HIPAA

The provision of data to the FDA, the Mini-Sentinel Coordinating Center, and to the Collaborating Institutions is to support a public health activity that is permitted under the HIPAA Privacy Rule without patient authorization. The HIPAA Privacy Rule permits covered entities to disclose PHI for a variety of public health purposes, including to:

[A] public health authority that is authorized by law to collect or receive such information for the purpose of preventing or controlling disease, injury, or disability, including, but not limited to, the reporting of disease, injury, vital events such as birth or death, and the conduct of public health surveillance, public health investigations, and public health interventions; or, at the direction of a public health authority, to an official of a foreign government agency that is acting in collaboration with a public health authority.⁶

The FDA is a “public health authority” under HIPAA, which is defined as:

an agency or authority of the United States, a State, a territory, a political subdivision of a State or territory, or an Indian tribe, or a person or entity acting under a grant of authority from or contract with such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate.⁷

The release of PHI to the FDA for purposes of drug safety surveillance is for the “conduct of public health surveillance” purposes, as contemplated by the rule.⁸

Moreover, the Mini-Sentinel Coordinating Center and its subcontractors (the Collaborating Institutions) are functioning as “public health authorities,” as well, because they are acting under contract with or under a grant of authority from the FDA. The Mini-Sentinel Coordinating Center is performing its functions under contract with the FDA. Moreover, even though the Collaborating Institutions do not have a direct contract with the FDA, FDA has

⁶ 45 C.F.R. §164.512(b)(1)(i).

⁷ 45 C.F.R. §164.501 (emphasis added).

⁸ “[T]he Privacy Rule specifically permits covered entities (such as pharmacists, physicians or hospitals) to report adverse events and other information related to the quality, effectiveness and safety of FDA-regulated products both to the manufacturers and directly to FDA.” See <http://www.fda.gov/medwAtch/hipaa.htm> (citing HHS Office for Civil Rights Guidance Explaining Significant Aspects of the Privacy Rule at page 28).

issued a letter to the Mini-Sentinel Coordinating Center explaining that both the Mini-Sentinel Coordinating Center and its subcontractors are acting under a grant of authority from the FDA. (See Exhibit 3.) Thus, data sources may release PHI requested by the Mini-Sentinel Coordinating Center and the Collaborating Institutions as “public health authorities” for the purpose of the Mini-Sentinel pilot medical product safety surveillance queries.⁹

Where a disclosure of PHI is to a public health authority, the HIPAA Privacy Rule *does not* require the covered entity to have an IRB or Privacy Board determine whether the covered entity may make the disclosure.

B. The Mini-Sentinel Pilot Documentation Provides Required Verification of Identity and Authority to Request PHI

To disclose PHI to the FDA or an entity acting under a contract or other grant of authority from the FDA, data sources must confirm the recipient’s identity and that the recipient has the legal authority to request the PHI.¹⁰ A covered entity is entitled to rely on written confirmation on FDA letterhead that the Mini-Sentinel Coordinating Center and the Collaborating Institutions are acting on behalf of the FDA, and that they have the legal authority to request PHI for the Mini-Sentinel pilot.¹¹ FDA has issued a letter to the Mini-Sentinel Coordinating Center explaining that both the Mini-Sentinel Coordinating Center and the Collaborating Institutions are acting under a grant of authority from the FDA, pursuant to the legal authority provided by the FDAAA. (See Exhibit 3.)

⁹ The internal use of PHI by the Collaborating Institution would similarly be permitted under HIPAA. . . . See Barbara J. Evans, Authority of the Food and Drug Administration to Require Data Access and Control Use Rights in the Sentinal Data Network, 65 Food & Drug Law Journal 67-112 (2010);

¹⁰ 45 C.F.R. § 164.514(h)(1)(i).

¹¹ 45 C.F.R. § 164.514(h)(2)(ii)(C) (allowing a covered entity, when making disclosure to a person acting on behalf of a public official, to rely on “a written statement on appropriate governmental letterhead that the person is acting under the government’s authority or other evidence or documentation of the agency, such as a contract for services . . . that establishes that the person is acting on behalf of the public official”; 45 C.F.R. § 164.514(h)(2)(iii)(A) (permitting a covered entity to rely on the written statement of a public agency regarding the legal authority under which it is requesting PHI, or an oral statement if a written statement is impracticable).

The Preamble to the Privacy Rule explained further: “For most disclosures, verifying the authority for the request means taking reasonable steps to verify that the request is lawful under this regulation. . . . Where the person requesting the protected information is a public official, covered entities must verify the identity of the requester by examination of reasonable evidence, such as a written statement of identity on agency letterhead, an identification badge, or similar proof of official status. . . . Similarly, covered entities are required to verify the legal authority supporting the request by examination of reasonable evidence, such as a written request provided on agency letterhead that describes the legal authority for requesting the release. . . . In some circumstances, a person or entity acting on behalf of a government agency may make a request for disclosure of protected health information under these subsections. . . . For example, public health agencies may contract with a nonprofit agency to collect and analyze certain data. . . . In such cases, the covered entity is required to verify the requestor’s identity and authority through examination of reasonable documentation that the requestor is acting on behalf of a government agency. . . . Reasonable evidence includes a written request provided on agency letterhead that describes the legal authority for requesting the release and states that the person or entity is acting under the agency or authority.” 65 Fed. Reg. at 82547 (emphasis added).

In other words, the data sources are not expected to make their own independent inquiry into whether queries from the FDA, the Mini-Sentinel Coordinating Center or the Collaborating Institutions serve a legally authorized public health purpose.

C. A Data Use Agreement Is Not Required for Disclosure to a Public Health Authority

Where the disclosure of PHI is to a public health authority, the HIPAA Privacy Rule does not require the recipient to sign a Data Use Agreement. The HIPAA Privacy Rule does permit a covered entity to release a “Limited Data Set” (partially de-identified data) for public health, research and health care operations purposes, as long as the covered entity first obtains a Data Use Agreement with the recipient of the Limited Data Set.¹² This rule permits the release of a Limited Data Set to entities that are not “public health authorities” under HIPAA, but that are using it for public health purposes. However, if the disclosure of PHI is to a “public health authority,” that disclosure does not need to be limited to a Limited Data Set nor requires a Data Use Agreement. Rather, covered entities may release fully-identifiable PHI to public health authorities.¹³

D. The Mini-Sentinel Pilot Documentation Meets Data Source Obligations to Comply with the Minimum Necessary Standard

HIPAA covered entities must observe the “minimum necessary standard” in releasing PHI for public health purposes. This simply means that a covered entity must make reasonable efforts to limit the information to the minimum amount of information that is necessary to accomplish the intended purpose of the disclosure,¹⁴ with some limited exceptions not relevant here.¹⁵ A covered entity may not disclose the entire medical record unless there is a specific justification for doing so.¹⁶

Under the HIPAA Privacy Rule, a covered entity may rely on a public health authority’s determination that the data requested are the minimum necessary data that the agency needs to fulfill the purpose of its request.¹⁷ When FDA (or the Coordinating Center or Collaborating Institutions acting on behalf of FDA) sends a query to a covered entity, Mini-Sentinel policies require the request to be limited to what is required to evaluate the drug safety issue. Covered

¹² 45 C.F.R. § 164.514(d).

¹³ 45 C.F.R. § 164.512(b).

¹⁴ 45 C.F.R. § 164.502(b)(1). . . .

¹⁵ 45 C.F.R. § 164.502(b)(2).

¹⁶ 45 C.F.R. § 164.514(d)(5). . . .

¹⁷ See 45 C.F.R. § 164.514(d)(3)(iii) (“A covered entity may rely, if such reliance is reasonable under the circumstances, on a requested disclosure as the minimum necessary for the stated purpose when: (A) Making disclosures to public officials that are permitted under § 164.512, if the public official represents that the information requested is the minimum necessary for the stated purpose.” While §13405(b) of the Health Information Technology for Economic and Clinical Health Act (the HITECH Act), codified at 42 U.S.C. § 17935, contains a provision that requires covered entities to determine what is the minimum amount of PHI for a disclosure, the proposed amendments to the HIPAA Privacy Rule to implement the HITECH Act do not modify a covered entity’s ability to rely on minimum necessary representations by public officials. . . . (See Notice of Proposed Rule Making, “Modifications to the HIPAA Privacy, Security, and Enforcement Rules under the [HITECH] Act,” at http://www.ofr.gov/OFRUpload/OFRData/2010-16718_PL.pdf, scheduled for publication in the Federal Register on July 14th.)

entities thus may rely on these public health authority requests as being limited to the minimum amount of PHI necessary for the Mini-Sentinel activities.

IV. Conclusion

Data source participation in the Mini-Sentinel pilot complies both with the Common Rule and HIPAA. OHRP has determined that Sentinel activities are not governed by the Common Rule. Moreover, the disclosure of PHI to the FDA, the Mini-Sentinel Coordinating Center and the Collaborating Institutions is disclosure of PHI to “public health authorities,” and thus does not require individual authorization or IRB approval.

Exhibit 1



DEPARTMENT OF HEALTH & HUMAN SERVICES

Office of the Secretary
Office of Public Health and Science

Office for Human Research Protections
Rockville, Maryland 20852

JAN 19 2010

Rachel E. Behrman, M.D., M.P.H.
Acting Associate Director of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration
Bldg 22, Room 4208
10903 New Hampshire Avenue
Silver Spring, Maryland 20993

Dear Dr. Behrman:

The Office for Human Research Protections has determined that the regulations this office administers (45 CFR part 46) do not apply to the activities that are included in the Food and Drug Administration's Sentinel Initiative.

Do not hesitate to contact us if we can be of any further assistance.

Sincerely,

Jerry Menikoff, M.D., J.D.
Director
Office for Human Research Protections

cc: Joanne Less, FDA

Exhibit 2



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Ave
Silver Spring, MD 20993

April 2, 2010

Dr. Richard Platt
Professor and Chair of the Department of Ambulatory Care and Prevention
Harvard Medical School and Harvard Pilgrim Health Care
133 Brookline Ave
Boston, MA 02215

Dear Dr. Platt:

The attached letter from the Office for Human Research Protections states: "The Office for Human Research Protections has determined that the regulations this office administers (45 CFR Part 46) do not apply to the activities that are included in the Food and Drug Administration's Sentinel Initiative."

This assessment applies to the work being conducted by you and your subcontractors under contract number HHSF2232009100061, as the purpose of this contract is to carry out activities that are included in the Food and Drug Administration's Sentinel Initiative.

Please let me know if you have any questions.

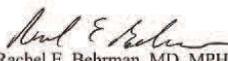

Rachel E. Behrman, MD, MPH
Sentinel Initiative, Executive Sponsor

Exhibit 3



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
10903 New Hampshire Ave.
Silver Spring, MD 20993

July 19, 2010

Dr. Richard Platt

Professor and Chair of the Department of Ambulatory Care and Prevention
Harvard Medical School and Harvard Pilgrim Health Care
133 Brookline Ave
Boston, MA 02215

Re: HIPAA Compliance for Data Sources Participating in the Mini-Sentinel Pilot Project

Dear Dr. Platt:

This letter affirms that the activities performed by the Mini-Sentinel Coordinating Center (MSCC) and its Collaborating Institutions,¹ in fulfillment of contract number HHS F2232009100061, are

¹ The Collaborating Institutions include:

1. America's Health Insurance Plans (AHIP)
2. Brigham and Women's Hospital Division of General Medicine
3. Brigham and Women's Hospital Division of Pharmacoepidemiology & Pharmacoeconomics
4. CIGNA Healthcare
5. Cincinnati Children's Hospital Medical Center
6. Columbia University Department of Statistics
7. Critical Path Institute (C-Path)
8. Duke University School of Medicine
9. HealthCore, Inc.
10. HMO Research Network including: Group Health Research Institute (GHRI) at the University of Washington (UW); Harvard Pilgrim Health Care Institute (HPHCI); Health Partners Research Foundation; Henry Ford Health Systems; Lovelace Clinic Foundation; Marshfield Clinic Research Foundation; Meyers Primary Care Institute (Fallon)
11. Humana-Miami Health Services Research Center (HSRC)
12. Kaiser Permanente Center for Safety and Effectiveness Research (CESR) including: Northern California (KPNC); Southern California (KPSC); Colorado (KPCO); Northwest (KPNW); Georgia (KPSE); Hawaii (KPHI); Ohio (KPOhio); MidAtlantic (KPMidAtlantic)
13. Outcome Sciences, Inc. (Outcome)
14. Risk Sciences International (RSI)
15. Rutgers University Institute for Health
16. University of Alabama at Birmingham (UAB)



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Silver Spring, MD 20993

public health activities for which HIPAA permits covered entities to disclose Protected Health Information (PHI) without individual authorization and without the need to obtain approval by or waiver of HIPAA authorization from an Institutional Review Board or Privacy Board.

The HIPAA Privacy Rule, at 45 C.F.R. § 164.512(b)(1)(i), permits covered entities to disclose PHI to a public health authority. The FDA is a public health authority, and has legal authority under Section 905 of the Food and Drug Administration Amendments Act of 2007 (Pub. L. No. 110-85) to conduct activities related to the project entitled, *Detection and Analysis of Adverse Events related to Regulated Products in Automated Healthcare Data. Efforts to Develop the Sentinel Initiative* (the Mini-Sentinel pilot project).

Under 45 C.F.R. § 164.501, a "public health authority" includes the FDA and "a person or entity acting under a grant of authority from or contract with" the FDA. Harvard Pilgrim Health Care is acting under the above-referenced contract with FDA to operate the MSCC. The Collaborating Institutions are under subcontract to Harvard Pilgrim Health Care to conduct activities in furtherance of FDA's Mini-Sentinel pilot project. As such, MSCC and the Collaborating Institutions are all acting under a grant of authority from FDA and have the status of public health authorities under the HIPAA Privacy Rule for purposes of carrying out their responsibilities under the Mini-Sentinel pilot project.

HIPAA covered entities are required to verify that a person requesting PHI for public health purposes is a public health authority. For this purpose, HIPAA covered entities are entitled to rely on a written statement on appropriate government letterhead that the person is acting under the government's authority (see 45 C.F.R. § 164.514(h)(2)(ii)(C)). This letter serves to provide the necessary written statement of authority to the MSCC and the Collaborating Institutions.

The HIPAA Privacy Rule also requires covered entities to comply with the minimum necessary rule at 45 C.F.R. § 164.502, but permits covered entities to rely on representations by a public health authority that it is requesting only the minimum amount of PHI necessary to carry out its public health mission (see 45 C.F.R. 164.514(d)(3)(iii)(A)). The Mini-Sentinel pilot project policies require MSCC and the Collaborating Institutions to request only the minimum necessary information that is required for purposes of carrying out their responsibilities. Thus, HIPAA covered entities may determine that requests from the MSCC and its Collaborating Institutions meet the minimum necessary standard.

Finally, because disclosures of PHI for the Mini-Sentinel pilot project are for public health activities, it is not necessary for HIPAA covered entities to obtain approval by their IRBs or

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- 17. University of Illinois at Chicago (UIC)
 - 18. University of Iowa, College of Public Health
 - 19. University of Pennsylvania School of Medicine
 - 20. Vanderbilt University School of Medicine
 - 21. Weill Cornell Medical College



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waiver of HIPAA authorization to provide data for Mini-Sentinel. The HHS Office for Human Research Protections (OHRP) has concluded that the regulations found in 45 CFR Part 46 (the "Common Rule") do not apply to activities related to the Sentinel Initiative and thus review by an IRB is not required by that rule.

A handwritten signature in blue ink that reads "Rachel Behrman".

Rachel E. Behrman, MD, MPH
Sentinel Initiative, Executive Sponsor

June 10, 2011

Dear Mini-Sentinel Data Partners,

This letter affirms that all Harvard Pilgrim Health Care, Inc. (HPHC) subcontractors that perform services for HPHC in fulfillment of contract number HHSF2232009100061 (the FDA Mini-Sentinel pilot), are subject to the same contractual requirements concerning the privacy and confidentiality of commercial confidential information and health care data, including but not limited to protected health information (PHI), as are subcontractors that are named as Collaborating Institutions. All subcontractors are likewise subject to the provisions of the Mini-Sentinel statement of Principles and Policies. A current list of Mini-Sentinel subcontractors is available from the Operations Center.

Please contact Susan Forrow with questions or concerns.



Richard Platt, MD, MSc
Mini-Sentinel Principal Investigator
Harvard Pilgrim Health Care Institute
Boston, MA



DEPARTMENT OF HEALTH & HUMAN SERVICES

Food and Drug Administration
Center for Drug Evaluation & Research

June 10, 2011

Dear Mini-Sentinel Data Partners,

Organizations that participate in the FDA Mini-Sentinel pilot project as contractors and subcontractors serve as “public health authorities” in performance of Mini-Sentinel work because they are engaged in public health surveillance activities under a grant of authority from the FDA.¹ The attached letter that I sent to Richard Platt, Mini-Sentinel Principal Investigator, explains the legal reasoning behind the allocation of public health authority status to Mini-Sentinel contractors and subcontractors.

This letter affirms that all Harvard Pilgrim Health Care, Inc. (HPHC) subcontractors that provide services to HPHC in fulfillment of contract number HHSF2232009100061 (the FDA Mini-Sentinel pilot), are covered by this FDA grant of authority, whether or not they are specifically listed as Collaborating Institutions. All subcontractors are likewise subject to the provisions of the Mini-Sentinel statement of Principles and Policies, including those regarding confidentiality and data privacy. A current list of Mini-Sentinel subcontractors is available from the Operations Center.

The HIPAA Privacy Rule permits covered entities to disclose protected health information (PHI) to public health authorities without patient authorization. Because Mini-Sentinel subcontractors are public health authorities, it is not necessary for Data Partners to obtain approval from their respective Institutional Review Boards (IRBs) or Privacy Boards, or to obtain waivers of authorization under HIPAA, to provide data to any Mini-Sentinel subcontractors in the conduct of Mini-Sentinel activities ([45 CFR §164.512\(b\)](#)). Please contact [Susan Forrow](#) at the Harvard Pilgrim Health Care Institute (HPHCI) with questions or concerns.



Rachel Behrman Sherman, MD, MPH
Associate Director for Medical Policy
Center for Drug Evaluation and Research
U.S. Food and Drug Administration
Sentinel Initiative, Executive Sponsor

¹ See Rosati, K., Evans, B., and McGraw, D., [HIPAA and Common Rule Compliance in the Mini-Sentinel Pilot](#), White Paper, July 2010.



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July 19, 2010

Dr. Richard Platt

Professor and Chair of the Department of Ambulatory Care and Prevention

Harvard Medical School and Harvard Pilgrim Health Care

133 Brookline Ave

Boston, MA 02215

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6. Columbia University Department of Statistics
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8. Duke University School of Medicine
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public health activities for which HIPAA permits covered entities to disclose Protected Health Information (PHI) without individual authorization and without the need to obtain approval by or waiver of HIPAA authorization from an Institutional Review Board or Privacy Board.

The HIPAA Privacy Rule, at 45 C.F.R. § 164.512(b)(1)(i), permits covered entities to disclose PHI to a public health authority. The FDA is a public health authority, and has legal authority under Section 905 of the Food and Drug Administration Amendments Act of 2007 (Pub. L. No. 110-85) to conduct activities related to the project entitled, *Detection and Analysis of Adverse Events related to Regulated Products in Automated Healthcare Data. Efforts to Develop the Sentinel Initiative* (the Mini-Sentinel pilot project).

Under 45 C.F.R. § 164.501, a "public health authority" includes the FDA and "a person or entity acting under a grant of authority from or contract with" the FDA. Harvard Pilgrim Health Care is acting under the above-referenced contract with FDA to operate the MSCC. The Collaborating Institutions are under subcontract to Harvard Pilgrim Health Care to conduct activities in furtherance of FDA's Mini-Sentinel pilot project. As such, MSCC and the Collaborating Institutions are all acting under a grant of authority from FDA and have the status of public health authorities under the HIPAA Privacy Rule for purposes of carrying out their responsibilities under the Mini-Sentinel pilot project.

HIPAA covered entities are required to verify that a person requesting PHI for public health purposes is a public health authority. For this purpose, HIPAA covered entities are entitled to rely on a written statement on appropriate government letterhead that the person is acting under the government's authority (see 45 C.F.R. § 164.514(h)(2)(ii)(C)). This letter serves to provide the necessary written statement of authority to the MSCC and the Collaborating Institutions.

The HIPAA Privacy Rule also requires covered entities to comply with the minimum necessary rule at 45 C.F.R. § 164.502, but permits covered entities to rely on representations by a public health authority that it is requesting only the minimum amount of PHI necessary to carry out its public health mission (see 45 C.F.R. 164.514(d)(3)(iii)(A)). The Mini-Sentinel pilot project policies require MSCC and the Collaborating Institutions to request only the minimum necessary information that is required for purposes of carrying out their responsibilities. Thus, HIPAA covered entities may determine that requests from the MSCC and its Collaborating Institutions meet the minimum necessary standard.

Finally, because disclosures of PHI for the Mini-Sentinel pilot project are for public health activities, it is not necessary for HIPAA covered entities to obtain approval by their IRBs or

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waiver of HIPAA authorization to provide data for Mini-Sentinel. The HHS Office for Human Research Protections (OHRP) has concluded that the regulations found in 45 CFR Part 46 (the "Common Rule") do not apply to activities related to the Sentinel Initiative and thus review by an IRB is not required by that rule.



Rachel E. Behrman, MD, MPH
Sentinel Initiative, Executive Sponsor



DEPARTMENT OF HEALTH & HUMAN SERVICES

**Food and Drug Administration
Center for Drug Evaluation & Research**

We are writing to ask your help with an important public health activity. The Food and Drug Administration (FDA) has initiated a chart validation activity of suspected anaphylaxis events in its Mini-Sentinel pilot. The goal of the project is to validate an algorithm for identifying anaphylaxis in electronic databases. While no specific medical product will be studied as part of this project, FDA expects to use this algorithm in future projects that assess potential medical product safety concerns related to this health event.

Mini-Sentinel is a pilot project sponsored by the [U.S. Food and Drug Administration \(FDA\)](http://www.fda.gov) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. For additional information on the FDA's Sentinel Initiative, please visit: <http://www.fda.gov/Safety/FDAsSentinelInitiative/default.htm>. For more information on Mini-Sentinel, please visit: <http://mini-sentinel.org/>.

FDA is requesting your help to obtain medical records for this project. Medical records are important because they will allow investigators to verify that your patient truly had anaphylaxis. To ensure privacy and confidentiality, all personal identifying information will be redacted (deleted) from the chart by the requesting Mini-Sentinel Data Partner and only the minimum necessary information will be shared with investigators to enable the completion of the project. Further, project investigators will share only de-identified, summary data and final analyses with the FDA.

All Mini-Sentinel activities are considered public health practice and not research. As such, this effort does not require Institutional Review Board review, since it is considered to be in support of FDA's public health mission. For more information, please see Mini-Sentinel's *Principles and Policies* document at: http://mini-sentinel.org/about_us/principles_and_policies.aspx. The relevant section is also copied below for ease of reference:

4.1 Mini-Sentinel Activities Are Public Health Practice, Not Research

The HHS Office of Human Research Protections (OHRP) determined that the regulations administered by OHRP (45 CFR Part 46, "Common Rule") do not apply to the activities that are included in the FDA's Sentinel Initiative. FDA stated that this assessment also applies to Mini-Sentinel, as it is part of the Sentinel Initiative.

Additionally, FDA determined that Mini-Sentinel activities are public health activities in support of FDA's public health mission. It is therefore

not necessary for the Collaborating Institutions to obtain approval from their respective Institutional Review Boards (IRBs) or Privacy Boards, or to obtain waivers of authorization under HIPAA, to participate in Mini-Sentinel activities (45 CFR §164.512(b)).

The HIPAA Privacy Rule permits covered entities the use and disclosure of protected health information (PHI) to public health authorities without patient authorization. Public health authorities include the FDA. The Operations Center and Collaborating Institutions are also public health authorities for purposes of the Mini-Sentinel pilot, because they are acting under contract with and under the authority of the FDA.

We very much appreciate your assistance with this important public health activity. FDA believes that the results will help better inform the Agency and healthcare providers worldwide. Please contact Azadeh Shoaibi, FDA's Project Lead, (azadeh.shoaibi@fda.hhs.gov), if you have questions or concerns about this letter, or Susan Farrow, Project Manager at Harvard Pilgrim Healthcare Institute (susan_farrow@harvardpilgrim.org), if you have further questions about the anaphylaxis validation project.

Sincerely,



Rachel E. Sherman, M.D., M.P.H.,
Associate Director of Medical Policy and
Director, Office of Medical Policy
Center for Drug Evaluation and Research
Food and Drug Administration

B. APPENDIX B. ANAPHYLAXIS VALIDATION EXTRACTION FORM AND MANUAL

ANAPHYLAXIS VALIDATION Data Partner Extraction Form and Checklist

Please complete the following form for **EACH and EVERY** case whose medical record you request, even if the record is not obtained. Upon completion, please attach this form to the redacted chart components and additional data elements specified below, and forward to the Mini-Sentinel Operations Center.

I. Extraction Information: General

1.	Case Identification Number:	
2.	Dates of Service:	___/___/___ through ___/___/___
3.	Extraction Date:	___/___/___

II. Chart Retrieval Status

1.	Were you able to obtain the chart for the specified case?	No (0)	Yes (1)
If Yes, skip to Part III of this form. If No, continue.			
2.	Why was the chart NOT obtained?		
	a. Chart is missing or not found	No (0)	Yes (1)
	b. Chart not sent to Data Partner	No (0)	Yes (1)
	c. IRB restricted chart retrieval	No (0)	Yes (1)
	d. Provider refusal and/or require patient consent	No (0)	Yes (1)
	e. Other: _____	No (0)	Yes (1)
STOP extraction and forward this form to the Mini-Sentinel Operations Center.			

III. Patient Identification Verification

1.	Name	No (0)	Yes (1)
2.	Date of Service from SAS code	No (0)	Yes (1)
3.	Actual Date of Service from medical record within 7 days before date specified by SAS code	No (0)	Yes (1)
4.	Date of Birth (DOB)	No (0)	Yes (1)
5.	Sex	No (0)	Yes (1)
6.	Do you have the correct chart?	No (0)	Yes (1)
If Yes, continue to Part IV of this form. If No, STOP extraction and forward this form to the Mini-Sentinel Operations Center.			

IV. Attachments: Chart Components

Emergency Room				
1.	All Emergency room notes		No (0)	Yes (1)
2.	All EMT/ambulance notes		No (0)	Yes (1)
3.	All orders		No (0)	Yes (1)
4.	Nursing medication administration record		No (0)	Yes (1)
5.	All available information on vital signs (heart rates, blood pressures, temperature, respiration rate, pulse oxygenation level)		No (0)	Yes (1)
6.	Allergy list		No (0)	Yes (1)
7.	Transfer note (if applicable)	N/A (2)	No (0)	Yes (1)
Inpatient				
1.	Physician notes (including history and physical notes, discharge summaries, progress notes, consult notes, death notes)		No (0)	Yes (1)
2.	All orders		No (0)	Yes (1)
3.	Nursing medication administration record		No (0)	Yes (1)
4.	All available information on vital signs (heart rates, blood pressures, temperature, respiration rate, pulse oxygenation level)		No (0)	Yes (1)
5.	Allergy list		No (0)	Yes (1)
6.	Transfer note (if applicable)	N/A (2)	No (0)	Yes (1)
<i>If patient was admitted through the ER also include:</i>				
7.	Copies of all items in ER list above	N/A (2)	No (0)	Yes (1)
Outpatient				
1.	All clinician notes from the visit date		No (0)	Yes (1)
2.	All EMT/ambulance notes (if applicable)	N/A (2)	No (0)	Yes (1)
3.	All vitals from the visit date		No (0)	Yes (1)
4.	All orders from the visit date		No (0)	Yes (1)
5.	Medication administration record, if any medications administered in clinic	N/A (2)	No (0)	Yes (1)
6.	Allergy list		No (0)	Yes (1)
7.	Outpatient allergist notes from 30 days after the visit date		No (0)	Yes (1)

STOP. Extraction is complete. Please attach this form to the redacted chart components and additional data elements requested and forward to the Mini-Sentinel Operations Center.

Thank you.

ANAPHYLAXIS VALIDATION

Instruction Manual for Completing Data Partner Extraction Form

The purpose of the Data Partner Extraction Form is to collect data from the chart to use in the validation of discharge diagnosis codes for anaphylaxis.

NOTE: The Data Partner Extraction Form should be completed for **EACH and EVERY** case for which you seek to obtain the chart. If you are unable to obtain the chart for any reason (noted under Part II) or if you determine that you do not have the correct chart (determined in Part III), the form should be forwarded along to the Mini-Sentinel Operations Center without any additional materials.

I. Extraction Information: General

Please provide the following information on the Data Partner Extraction Form:

1. Case Identification Number:
An internally generated ID code that will allow the Data Partner to link back to original records but will not be identifiable beyond the Data Partner.
2. Dates of Service:
Start and end dates of service from the chart in the format MM/DD/YYYY.
3. Extraction Date:
Date the extraction of the chart was completed in the format MM/DD/YYYY.

II. Chart Retrieval Status

Please circle “Yes” or “No” for each item and provide any requested information.

1. Were you able to obtain the chart for the specified case?
If yes, skip to Part III.
If no, continue.
2. Why was the chart NOT obtained?
 - a. Chart is missing or not found
 - b. Chart not sent to Data Partner
 - c. IRB restricted chart retrieval
 - d. Provider refusal and/or require patient consent
 - e. Other (please specify)

STOP data extraction and forward this form to the Mini-Sentinel Operations Center.

III. Patient Identification Verification

Please compare the information on the chart to your administrative data and verify that each item listed in 1-5 is the same. Circle one response, “Yes” or “No,” for each item.

1. Name
Indicate “Yes” if the patient name is the same in the chart and in the administrative data. Indicate “No” if the patient name is different.
2. Date of Service:
This item relates to the date the patient was seen in the emergency room or outpatient setting and/or admitted as an inpatient. Indicate “yes” if the date of service is the same in the chart as specified in the administrative data. Indicate “no” if the date of service is different in the chart than specified in the administrative data.
3. Actual Date of Service (within 7 days before date specified by SAS code):
Indicate if the date specified in the administrative data is within 7 days before date of service in the chart.
4. Date of Birth (DOB):
Indicate “Yes” if patient DOB is the same in the chart as it is in the administrative data. Indicate “No” if patient DOB is different.
5. Sex:
Indicate “Yes” if patient sex is the same in the chart as it is in the administrative data. Indicate “No” if patient sex is different.
6. Do you have the correct chart?
If yes, continue on to Part IV.

*If no, **STOP**. If the chart information does not correspond with administrative data and it seems that you do not have the correct chart, indicate “No” and do not proceed to next section. Stop data extraction and forward this form to the Mini-Sentinel Operations Center.*

IV. Attachments: Chart Components

Please obtain, redact*, and forward to the Mini-Sentinel Operations Center all of the chart components listed in this section from the entire encounter (please refer to Service Dates in Section I), indicating for each a “Yes” or “No” for its inclusion (in some cases “N/A” [not applicable] will be an option). Please write the case ID number on all attachments in the upper right hand corner.

***Do NOT redact the date that the physician progress notes were written, the dates and times the vital signs were recorded, the dates the orders were written, or the date of the medication record.**

Emergency Room	
1.	All Emergency room notes
2.	All EMT/ambulance notes
3.	All orders
4.	Nursing medication administration record
5.	All available information on vital signs (heart rates, blood pressures, temperature, respiration rate, pulse oxygenation level)
6.	Allergy list
7.	Transfer note (if applicable)
Inpatient	
1.	Physician notes (including history and physical notes, discharge summaries, progress notes, consult notes, death notes)
2.	All orders
3.	Nursing medication administration record
4.	All available information on vital signs (heart rates, blood pressures, temperature, respiration rate, pulse oxygenation level)
5.	Allergy list
6.	Transfer note (if applicable)
<i>If patient was admitted through the ER also include:</i>	
7.	Copies of all items in ER list above
Outpatient	
1.	All clinician notes from the visit date
2.	All EMT/ambulance notes (if applicable)
3.	All vitals from the visit date
4.	All orders from the visit date
5.	Medication administration record, if any medications administered in clinic
6.	Allergy list
7.	Outpatient allergist notes from 30 days after the visit date

STOP. Data extraction is complete. Please attach the Data Partner Extraction Form to the redacted chart components and additional data elements requested and forward to the Mini-Sentinel Operations Center.

C. APPENDIX C. ANAPHYLAXIS VALIDATION ABSTRACTION FORM

Case ID: _____

Mini-Sentinel: Anaphylaxis Validation Abstraction Form

Instructions: This form is for use in validation of discharge diagnosis codes for anaphylaxis.
See Instruction Manual for detailed guidelines for each form item.

****For inpatient charts, focus your detailed abstraction on the first 48 hours****

Abstractor's Initials

Abstraction Date / /

Case ID: _____

Section 1: General information

1. Was this an inpatient visit? YES
 NO

If YES, record admission and discharge dates as well as discharge status below:

1a. Date of admission: ___ / ___ / _____

1b. Date of discharge: ___ / ___ / _____

UNKNOWN

1c. Discharged to:

HOME

DIED

OTHER: _____

****Focus on first 48 hours****

2. Was this an emergency department visit? YES
 NO

If YES, record admission and discharge dates as well as discharge status below:

2a. Date of visit: ___ / ___ / _____

2b. Date of discharge: ___ / ___ / _____

UNKNOWN

2c. Discharged to:

HOME

ADMIT

DIED

OTHER: _____

3. Was this an outpatient visit? YES
 NO

If YES, record date of visit as well as discharge status below:

3a. Date of visit: ___ / ___ / _____

UNKNOWN

3b. Discharged to:

HOME

ADMIT

OTHER: _____

Case ID: _____

8. Was there exposure to a known or likely allergen?

YES
 NO

8a. If YES, please record the approximate date and time.

Approx. Date: ____/____/____
 M M D D Y Y Y Y
 UNKNOWN

Approx. Time: ____:____ (military time)
 UNKNOWN

8b. If YES, what was the time frame between exposure and onset of symptoms?

MINUTES
OR
 HOURS
OR
 DAYS

8c. List the known or likely allergen: _____

8d. If applicable, please describe why the allergen is considered likely: _____

9. Was there a documented acute episode (minutes to several hours) of symptoms consistent with involvement of skin, mucosal tissue or both within 8 hours of the exposure (if known) or of presentation if no known exposure? (Symptoms include: generalized hives, pruritis, flushing, swollen lips-tongue-uvula)

YES
 NO
 UNKNOWN

Case ID: _____

SKIN FINDINGS

10. Were there skin signs or symptoms?	<input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> UNKNOWN
10a. What were the skin findings?	<input type="checkbox"/> HIVES <input type="checkbox"/> PRURITIS <input type="checkbox"/> FLUSHING RASH (describe): _____ OTHER (describe): _____
10b. Describe skin findings:	_____ _____

MUCOSAL FINDINGS

11. Were there mucosal signs or symptoms?	<input type="checkbox"/> YES <input type="checkbox"/> NO <input type="checkbox"/> UNKNOWN
11a. What were the mucosal findings?	<input type="checkbox"/> RED, SWOLLEN EYES <input type="checkbox"/> SWOLLEN TONGUE, LIPS, UVULA <input type="checkbox"/> TIGHT THROAT OTHER (describe): _____

Case ID: _____

RESPIRATORY FINDINGS

12. Were there respiratory signs/symptoms within 8 hours of the exposure (if known) or of presentation if no known exposure?

YES
 NO
 UNKNOWN

12a. What were the respiratory findings?

DYSPNEA/SHORTNESS OF BREATH
 WHEEZE
 STRIDOR
 REDUCED PEAK EXPIRATOR FLOW
 APNEA
 HYPOXEMIA
 RESPIRATORY ARREST
 COUGH
 OTHER (describe): _____

BLOOD PRESSURE FINDINGS

13. Was there reduced blood pressure within 8 hours of the exposure (if known) or of presentation if no known exposure?

Aged 1 month – 1 year: Systolic BP <70
Aged 1 – 10 years: (70 mm Hg + [2 x age]) (This is a rough estimate, need height for accurate BP)
Aged over 11 years: Systolic BP <90

YES
 NO
 UNKNOWN

13b. If YES, how many low systolic blood pressures were there within the 8 hours of the exposure or of onset of symptoms?

1
 2
 3
 4
 MORE THAN 4

14. Were there symptoms of end-organ dysfunction?

YES
 NO
 UNKNOWN

14a. What were the end-organ dysfunction findings?

SYNCOPE
 INCONTINENCE
 CARDIAC ARREST
 CHANGE IN LEVEL OF ALERTNESS
 UTERINE CRAMPING
 OTHER (describe): _____

Case ID: _____

GASTROINTESTINAL FINDINGS

15. Were there gastrointestinal symptoms within 6-8 hours of the exposure (if known) or of presentation if no known exposure?

YES
 NO
 UNKNOWN

15a. What were the gastrointestinal findings?

ABDOMINAL PAIN
 ABDOMINAL CRAMPING
 VOMITING
 DIARRHEA
 OTHER (describe): _____

16. Does the patient have a past history of anaphylaxis?

YES
 NO
 UNKNOWN

17. Does the patient have a history of food or medication allergy?

YES
 NO
 UNKNOWN

18. Does the patient have a past history of asthma?

YES
 NO
 UNKNOWN

19. Does the patient have a past history of allergic rhinitis?

YES
 NO
 UNKNOWN

20. Does the patient have a past history of atopic dermatitis?

YES
 NO
 UNKNOWN

Case ID: _____

Section 3: Vital Signs

21. Record vital signs below as described below.

___ NONE AVAILABLE

Instructions: Please list blood pressure measured most immediately after exposure and within 8 hours of exposure. If no known exposure, please list vital signs upon presentation to the hospital and within 8 hours of presentation.

	Date (mm/dd/yyyy)	Time (military)	BP Systolic/diastolic	Temperature	Heart Rate	Respiratory rate	Oxygen saturation
a.	/ /	:	/				
b.	/ /	:	/				
c.	/ /	:	/				
d.	/ /	:	/				
e.	/ /	:	/				
f.	/ /	:	/				
g.	/ /	:	/				
h.	/ /	:	/				
i.	/ /	:	/				
j.	/ /	:	/				
k.	/ /	:	/				
l.	/ /	:	/				
m.	/ /	:	/				
n.	/ /	:	/				
o.	/ /	:	/				
p.	/ /	:	/				
q.	/ /	:	/				
r.	/ /	:	/				
s.	/ /	:	/				

Case ID: _____

Section 4: Medications Administered

22. Was epinephrine administered (oral, intramuscular or subcutaneous) within 8 hours of the exposure (if known) or of presentation if no known exposure?

YES
 NO
 UNKNOWN

23. Was albuterol administered within 8 hours of the exposure (if known) or of presentation if no known exposure?

YES
 NO
 UNKNOWN

24. Were oral or intravenous steroid administered within 8 hours of the exposure (if known) or of presentation if no known exposure?

YES
 NO
 UNKNOWN

25. Were H2 blockers administered (Famotidine (Pepcid), Diphenhydramine (Benadryl)) within 8 hours of the exposure (if known) or of presentation if no known exposure?

YES
 NO
 UNKNOWN

26. Were there other pertinent medications given?

YES
 NO
 UNKNOWN

Please list: _____

27. Was oxygen administered?

YES
 NO
 UNKNOWN

28. Was the patient intubated?

YES
 NO
 UNKNOWN

Case ID: _____

29. Was the patient given a tracheostomy?

YES
 NO
 UNKNOWN

30. Did the patient require chest compressions?

YES
 NO
 UNKNOWN

31. Other pertinent treatment?

YES
 NO
 UNKNOWN

If YES, list: _____

Section 5: Disposition

32. Discharge status

ALIVE
 DEAD (cause of death if noted) _____
32a. Patient dead on arrival
32b. Patient died in the emergency room
32c. Other/Unknown
 UNKNOWN

33. Was patient transferred to another hospital?

YES
 NO
 UNKNOWN

Section 6: Post-mortem (ONLY COMPLETE IF DEAD)

34. Was an autopsy performed?

YES (attach copy of report)
 NO
 UNKNOWN

Case ID: _____

Section 7: Inpatient stays >48hours

35. For inpatient stays >48 hours, was anaphylaxis or an allergic reaction documented in the first 48 hours?

YES
 NO

36. If NO, in your review of the rest of the chart, was there ever any mention of anaphylaxis or an allergic reaction occurring after the first 48 hours?

YES
 NO

If YES, please record date of first documentation and page number below:

_____ Date of first documentation

_____ Page #

D. APPENDIX D. ANAPHYLAXIS VALIDATION ADJUDICATION FORM

**MINI-SENTINEL: ANAPHYLAXIS VALIDATION
2012 ADJUDICATION FORM**

CASE ID: _____ **DATE OF REVIEW:** //
Adjudicator Initials: _____

CRITERIA FOR HIGHLY LIKELY ANAPHYLAXIS*
CHECK IF PRESENT:

- Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:**
 - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
- Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):**
 - Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue uvula)
 - Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
 - Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
- Reduced BP after exposure to known allergen for that patient (minutes to several hours):**
 - Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
 - Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP

EVENT CLASSIFICATION

DOES THIS PATIENT MEET THE CLINICAL CRITERIA FOR A DIAGNOSIS OF ANAPHYLAXIS?

- _____ **YES ANAPHYLAXIS**
- _____ **NO ANAPHYLAXIS**
- _____ **UNABLE TO DETERMINE**
- _____ **WHAT DATA WERE NEEDED BUT NOT AVAILABLE?**

IN YOUR CLINICAL OPINION, DOES THIS PATIENT HAVE ANAPHYLAXIS?

- _____ **YES ANAPHYLAXIS**
- _____ **NO ANAPHYLAXIS**
- _____ **UNABLE TO DETERMINE**

If your assessment based upon your clinical opinion differs from the anaphylaxis criteria outlined above (e.g., if the patient meets the criteria for anaphylaxis but in your clinical opinion the patient was likely not a case of anaphylaxis), please indicate rationale: _____

TABLE I. Clinical Criteria for Diagnosing Anaphylaxis¹

Anaphylaxis is highly likely when any of the following 3 criteria are fulfilled:

1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (eg, generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:
 - a. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - b. Reduced BP or associated symptoms of end-organ dysfunction (eg, hypotonia [collapse], syncope, incontinence)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):
 - a. Involvement of the skin-mucosal tissue (eg, generalized hives, itch-flush, swollen lips-tongue uvula)
 - b. Respiratory compromise (eg, dyspnea, wheeze-bronchospasm, stridor, reduced PEF, hypoxemia)
 - c. Reduced BP or associated symptoms (eg, hypotonia [collapse], syncope, incontinence)
 - d. Persistent gastrointestinal symptoms (eg, crampy abdominal pain, vomiting)
3. Reduced BP after exposure to known allergen for that patient (minutes to several hours):
 - a. Infants and children: low systolic BP (age specific) or greater than 30% decrease in systolic BP*
 - b. Adults: systolic BP of less than 90 mm Hg or greater than 30% decrease from that person's baseline BP

Abbreviations: PEF, Peak expiratory flow; BP, blood pressure.

*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.

¹Sampson HA, Munoz-Furlong A, Campbell RL, et al. Second symposium on the definition and management of anaphylaxis: summary report--Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium. *J Allergy Clin Immunol.* Feb 2006;117(2):391-397.