VALIDITY OF DIAGNOSTIC CODES TO IDENTIFY CASES OF SEVERE ACUTE LIVER INJURY 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.

Validity Of Diagnostic Codes To Identify Cases Of Severe Acute Liver Injury In The Mini-Sentinel Distributed Database

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I. EXECUTIVE SUMMARY

A. OVERVIEW OF PROJECT AND SUMMARY OF FINDINGS

Severe acute liver injury (SALI) associated with medical products is an important public health concern. The validity of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes to identify cases of SALI is not well known. This project examined the positive predictive values (PPVs) of hospital ICD-9-CM diagnoses in identifying SALI events separately among health plan members in the Mini-Sentinel Distributed Database (MSDD) without pre-existing liver/biliary disease and for those with chronic liver disease (CLD).

We selected random samples of members from five Mini-Sentinel Data Partners within the MSDD who had a principal hospital diagnosis indicative of SALI (ICD-9-CM codes 570 [acute hepatic necrosis], 572.2 [hepatic coma], 572.4 [hepatorenal syndrome], 572.8 [liver disease sequelae], 573.3 [toxic hepatitis], 573.8 [other specified liver disorder], V42.7 [liver transplant]) recorded between 2009 and 2010 and either no liver/biliary disease or prior CLD. Medical records were obtained and reviewed by hepatologists to confirm SALI cases. PPVs of codes and code combinations for confirmed SALI were determined separately among members without liver/biliary disease and with CLD.

Records were requested for 149 members with a principal hospital SALI ICD-9-CM diagnosis and no liver/biliary disease. Among 105 members with available medical records, SALI was confirmed in 26 (PPV, 24.7%; 95% CI, 16.9% – 34.1%). The presence of a hospital diagnosis of both acute hepatic necrosis (570) and liver disease sequelae (572.8) had high PPV (100%; 95% CI, 59.0% – 100%) and captured the highest proportion of events (7/26 [26.9%]) among the diagnostic coding algorithms evaluated. Records were also requested for 75 members with CLD and a principal hospital SALI diagnosis. Among 46 CLD members with available charts, SALI was confirmed in 19 (PPV, 41.3%; 95% CI, 27.0% – 56.8%). PPVs of individual SALI codes among CLD members were higher in magnitude than for cases without liver/biliary disease. The combination of a hospital diagnosis of either acute hepatic necrosis (570) or hepatorenal syndrome (572.4) plus any other SALI code had a PPV of 83.3% (95% CI, 51.6% - 97.9%) and identified ten (52.6%) of the 19 cases.

The individual pre-specified ICD-9-CM codes for identifying hospitalized SALI yielded a PPV of 24.8% for members without pre-existing liver/biliary disease and 41.3% for members with CLD. Select combinations of ICD-9-CM codes indicative of SALI had high PPV for confirmed outcomes among members without pre-existing liver/biliary disease and with CLD in the MSDD, but these algorithms identified only 4%-27% and 5%-53% of SALI cases, respectively. These algorithms could be used to detect SALI events in surveillance activities and in claims-based databases, but further validation would be prudent. Surveillance activities seeking to identify all possible SALI events using ICD-9-CM codes should consider confirming this endpoint on a case-by-case basis through medical record review.

II. BACKGROUND

Severe acute liver injury (SALI) is defined by the presence of impaired liver synthetic function.[1] SALI due to drug-induced hepatotoxicity is currently the second most frequent reason (after cardiac toxicity) for withdrawal of approved drugs.[2-5] Clinical trials are typically underpowered to detect uncommon (range, 1:1,000 to 1:10,000), but serious hepatic events.[2,6] As a result, drug-induced SALI might not be identified until after a product has been approved for use and taken by thousands of patients. To identify SALI in healthcare databases, validated definitions are needed. However, few studies have developed and validated methods to identify SALI in healthcare data.

Few studies have developed and validated methods to identify SALI within observational studies and in administrative claims-based and electronic health records databases.[7-9] The ability to identify SALI events accurately within electronic healthcare and administrative claims-based databases would greatly facilitate examinations of this outcome. This would have a major public health benefit by generating valid evidence on characterizing the hepatoxicity profile of medical products, greatly reducing medication-associated morbidity and enhancing medical product safety.

In 2008, the U.S. Food and Drug Administration (FDA) launched the Sentinel Initiative, a program designed to create a national electronic monitoring system for postmarketing risk identification and analysis of medical product safety that will use automated healthcare data to complement its existing surveillance systems.[10,11] The Mini-Sentinel pilot, a component of the Sentinel Initiative, is a collaborative effort between the FDA and more than 30 organizations.[12] Since accurate and timely identification of health outcomes is an essential component of active safety surveillance, Mini-Sentinel convened a workgroup comprised of clinicians, pharmacoepidemiologists, Mini-Sentinel Data Partners, Mini-Sentinel Operations Center (MSOC) representatives, and members of the FDA (Appendix A) to establish a process for identification and validation of SALI. We evaluated the ability of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes to identify cases of SALI (without regard for etiology) within the Mini-Sentinel Distributed Database (MSDD). The MSDD is a multi-site distributed data network designed to implement the Mini-Sentinel Common Data Model (MSCDM) that is being piloted to assess postmarketing safety issues with FDA-regulated products. It contains data on health plan member demographics, enrollment, location of encounter, outpatient pharmacy dispensing (recorded using National Drug Codes [NDC]), outpatient and hospital-associated medical diagnoses (recorded using ICD-9-CM diagnostic codes) and procedures (recorded using Current Procedural Terminology [CPT] codes), and date of death.[13] Several Data Partners also provide additional clinical and vital sign information, such as select laboratory results, weight, height, and blood pressure, to the MSDD.

Since the accuracy of these codes might be different based on pre-existing chronic liver/biliary disease status,[14] we first examined the positive predictive value (PPV) of these codes in identifying medical record-confirmed cases of SALI among health plan members without a prior diagnosis of a liver/biliary disease. We then evaluated their PPV among those with previously diagnosed chronic liver disease (CLD).

III. METHODS

A. OVERVIEW OF DESIGN FOR THE SALI VALIDATION PROCESS

We conducted a cross-sectional analysis among health plan members in the MSDD who had a principal hospital diagnosis suggestive of SALI recorded between January 1, 2009 and December 31, 2010. We utilized administrative and claims data from five MSDD Data Partners, representing a total of eight health plans (HealthCore, Inc.; HMO Research Network [HealthPartners Institute for Education and Research, Marshfield Clinic Research Foundation, Group Health Research Institute]; Humana; Kaiser Permanente Center for Effectiveness and Safety Research [Kaiser Permanente Colorado, Kaiser Permanente Northwest]; Vanderbilt University School of Medicine/TennCare Bureau).

In 2010, the Office for Human Research Protections (OHRP) at the Department of Health and Human Services determined that the Mini-Sentinel pilot constituted a public health surveillance activity not under the purview of the Institutional Review Board (IRB).[15] The Mini-Sentinel Privacy Panel assembled a privacy packet and the SALI workgroup distributed this packet to the eight participating Data Partner health plans in this validation.[16] The privacy packet contained letters from the OHRP, FDA, and Mini-Sentinel Principal Investigator Richard Platt explaining the reasoning and implications of Mini-Sentinel being considered public health surveillance, rather than research.

For the chart retrieval process, the Data Partners were given a letter template to send to their provider sites explaining: Mini-Sentinel Pilot program, its association with the FDA, and the determination that the project is public health surveillance (Appendix B). In addition to sending this letter, Data Partners were encouraged to submit the privacy packet to relevant medical records departments and IRBs of provider sites.

B. CASE IDENTIFICATION

In an effort to obtain sufficient sample sizes for analyses, we queried data from the MSDD from January 1, 2009 through December 31, 2010, inclusively. There were no restrictions on age, sex, or any other member characteristics, including continuous eligibility of prescription drug coverage. However, continuous health plan enrollment for 12 months (excluding gaps of ≤ 30 days) was required prior to the first appearance of a SALI code. Members were identified as having a SALI event by the presence of a principal ICD-9-CM hospital diagnosis code suggestive of possible toxic hepatitis or acute liver failure (ALF; Table 1). Selection of these diagnosis codes was based on discussions with collaborating hepatologists within the workgroup and results of prior observational studies that suggested that these codes were frequently recorded among cases with confirmed liver injury.[7,8] A random sample of members with these codes was selected for this workgroup activity.

The earliest date on which a SALI code was recorded for a member during the two-year period was considered the index date. For members who had a principal SALI diagnosis code recorded during the hospitalization but after the actual date of admission, the admission date was considered the SALI index date. Any individuals without an index date were excluded.

Table 1. List of International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes evaluated for their ability to identify potential cases of severe acute liver injury.

CODE	DESCRIPTION
Acute Liver Failure	
570	Acute and subacute necrosis of the liver
572.2	Hepatic coma
572.4	Hepatorenal syndrome
572.8	Sequelae of liver disease
V42.7	Liver replaced by transplant
Toxic Hepatitis	
573.3	Toxic (non-infectious) hepatitis
573.8	Other specified disorder of the liver

1. Members without pre-existing liver/biliary disease

After using the SALI event criteria described above, we identified members who also had: 1) no inpatient or outpatient ICD-9-CM diagnosis (in any position) of a pre-existing liver or biliary disease (i.e., alcoholic liver disease; non-alcoholic fatty liver disease; hepatitis B, C, D, or E; non-specific hepatitis or chronic unspecified liver disease; Wilson's disease; autoimmune hepatitis; hemochromatosis; cancer in the liver, biliary tree, or pancreas; alpha-1-antitrypsin deficiency; biliary tract obstruction and/or cholangitis; primary biliary cirrhosis; cirrhosis due to any cause; or hepatic decompensation [see Appendix C for code list and descriptions]) recorded within 12 months prior to the index date, and 2) no principal diagnosis codes suggestive of pre-existing liver/biliary disease (Appendix C) during the hospitalization associated with the index date.

The rationale for excluding members with a liver/biliary disease was to reduce the identification of SALI events due to these underlying conditions. Since we wished to develop a diagnostic coding algorithm that could ultimately be used to evaluate associations between medical products and SALI, the exclusion of these cases served to increase the likelihood that the identified SALI cases would be medical product-related.

To ensure sufficient sample sizes to evaluate the validity of inpatient toxic hepatitis and ALF ICD-9-CM diagnoses for medical record-confirmed SALI and to enable a separate determination of the accuracy of the ALF ICD-9-CM codes for confirmed ALF, we randomly sampled 75 members, within the five selected Data Partners, who had a principal hospital diagnosis that suggested possible toxic hepatitis (ICD-9-CM codes 573.3 or 573.8) and 74 with a principal inpatient diagnosis suggestive of possible ALF (ICD-9-CM codes 570, 572.2, 572.4, 572.8, or V42.7). Thus, we sampled 149 members with a principal hospital diagnosis code suggestive of SALI in the absence of pre-existing liver or biliary disease. The number of charts requested was initially divided among the Data Partners regardless of membership size, with each Data Partner selecting a similar number of cases with possible toxic hepatitis and ALF diagnoses. For the two Data Partners that had multiple health plans participating in this project, the number of charts within each of these two Partners was further divided based on membership size. There were some instances where a health plan had an insufficient number of members with the SALI diagnoses of

interest in their population. To reach the target sample size, additional members with SALI diagnoses were sampled from other participating Data Partners. For the two Data Partners that had multiple health plans participating in this project, one of the associated health plans was asked to retrieve the additional claims data if one of these health plans had an insufficient number of members with SALI diagnoses. For the three remaining Data Partners, if there were an insufficient number of members with SALI diagnoses, the other Data Partners were asked to obtain additional data at random.

2. Members with pre-existing chronic liver disease

To evaluate the validity of SALI diagnoses in members with pre-existing CLD, we identified members who also had at least two outpatient CLD ICD-9-CM diagnoses (see Appendix D for code list and descriptions) recorded on at least two separate dates within 12 months prior to the SALI diagnosis. We excluded members with a diagnosis of biliary tract obstruction or cancer in the liver, biliary tree, or pancreas (since our focus was on CLD) or with a diagnosis suggestive of hepatic decompensation (since such conditions indicate chronic liver failure) recorded within 12 months prior to the index date (see Appendix E for code list and descriptions).

We randomly sampled 75 CLD members, within the five selected Data Partners, with a principal hospital SALI diagnosis code (Table 1). The number of charts requested was again divided among the Data Partners using the same method as described for members without pre-existing liver/biliary diseases.

3. Main outcomes

The primary outcome was SALI, which was determined based on abnormalities of serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), total bilirubin, and/or international normalized ratio (INR). A diagnosis of SALI was confirmed for members without liver/biliary disease and with CLD if at any time during a hospitalization either of the following definitions was met: 1) ALT or AST >3 times upper limit of normal (ULN) + total bilirubin >2 times the ULN (definition 1), or 2) total bilirubin >2 times the ULN + INR $\geq$1.5, in the absence of anticoagulation therapy (definition 2). The ULNs for ALT, AST, and total bilirubin were determined by the assay from which each result was measured. The combination of biochemical abnormalities for each definition did not need to occur on the same day.

The rationale for definition 1 is that hepatocellular injury great enough to interfere with bilirubin excretion in a SALI case caused by drug-induced hepatotoxicity,, which represents Hy's Law,[17-19] involves a large fraction of the liver cell mass, indicates liver synthetic dysfunction, and predisposes a patient to a high risk of mortality.[20,21] The rationale for definition 2 is that some cases with SALI might present in an advanced stage of ALF, such that serum liver aminotransferases might not be as high as levels that meet definition 1. We did not include the subtype of bilirubin (i.e., direct, indirect) in either SALI definition, since it may not be measured in routine practice.

Elevations in alkaline phosphatase alone, without increases in ALT, AST, or total bilirubin, were not classified as SALI events because this finding may indicate cholestasis in the absence of SALI. Further, we did not perform a formal causality assessment for each SALI event (e.g., drug-induced). However, among cases that were confirmed to not have SALI, we did determine the potential etiology for their hospitalization.

As a secondary outcome among cases without pre-existing liver/biliary disease, we determined ALF, which represents the most serious clinical outcome of SALI.[22,23] A diagnosis of ALF was confirmed if, at

any time during the hospitalization, a member had: 1) coagulapathy, defined as INR ≥1.5 in the absence of anticoagulation therapy, and either 2a) hepatic encephalopathy, defined as altered mentation due to liver dysfunction, or 2b) orthotopic liver transplant due to ALF. This definition was based on those developed by the U.S. Acute Liver Failure Study Group and American Association for the Study of Liver Diseases.[22,24,25]

4. Program code to identify cases

Using the criteria described above, the MSOC, in collaboration with the SALI workgroup, developed a SAS program for the Data Partners to identify a total of 224 potential SALI cases for medical record review. Program code was tested, and a test run was conducted at two Data Partner locations to ensure accuracy prior to distribution to all Data Partners. Each Data Partner then executed the SAS program locally and provided the MSOC with the output via the Mini-Sentinel Secure Portal.

C. CHART RETRIEVAL

The workgroup used the case retrieval process established by the Acute Myocardial Infarction (AMI) Health Outcome of Interest Validation workgroup in Year 1 of the Mini-Sentinel Pilot Program.[26]

1. Determination of chart components

The workgroup collaboratively identified a listing of the minimal data elements and chart components needed for the validation of SALI. The requested chart components included the following: admission history and physical, discharge summary, transfer records, physician progress notes for all specialties, autopsy reports/death notes, liver biopsy pathology reports, laboratory reports, inpatient medication administration record, and head/brain imaging reports. All chart components were redacted of any data elements that directly identified individuals, but included dates of service.

The MSOC reviewed the list of requested chart components in relation to the HIPAA Privacy Rule's minimum necessary standard, and confirmed that the information requested constituted the minimum amount of information necessary for this project.

2. Obtaining chart information

Data Partners were provided with a privacy packet prepared by the Mini-Sentinel Privacy Panel which included: 1) the Mini-Sentinel Privacy Panel white paper discussing data privacy issues in Mini-Sentinel, 2) letters from OHRP to the FDA and from the FDA to the Mini-Sentinel Principal Investigator stating that the Sentinel and Mini-Sentinel activities, respectively, are not within OHRP's purview, and 3) letters from the FDA to the Mini-Sentinel Principal Investigator stating that the Mini-Sentinel is a public health activity under HIPAA.[16] Data Partners disseminated the privacy packet and provider request letter (Appendix B) to their Institutional Review Boards and Privacy Boards, as well as to all providers from which they were requesting charts.

Additionally, Data Partners were provided with a structured extraction form and checklist (Appendix F) with a corresponding manual (Appendix G). It was requested that Data Partners complete this form for each potential case whose medical record was requested, even if the record was not obtained. If the chart could not be obtained, Data Partners were asked to indicate any of the following reasons: 1) chart was missing or not found, 2) chart was not sent to the Data Partner, 3) IRB restricted chart retrieval, or 4) specify an alternate reason.

Selected cases were identified at each Data Partner using the previously described SAS program. Data Partners gathered potential cases' identifying information and determined the providers housing each of the requested charts. Charts were requested of the provider by the Data Partner directly or through a subcontract with a vendor. Various methods were used to retrieve and redact the chart components, including: 1) charts were retrieved by providers and sent to the Data Partner who performed redaction, 2) charts were retrieved at the provider site by the Data Partner's abstractor, who performed redaction, and 3) charts were retrieved at the hospital by a subcontracted vendor's abstractor, who performed redaction and forwarded an electronic copy to the Data Partner. These methods are discussed in detail in Appendix H. All redacted charts were submitted electronically to the Mini-Sentinel Secure Portal. The MSOC then made the charts available to the workgroup for abstraction and adjudication.

3. Collection of additional electronic data

For each member selected for medical record review, additional electronic data was collected by the program code from the MSDD. This information included the age of the member at the SALI index date, sex, and SALI classification group (i.e., toxic hepatitis without liver/biliary disease, ALF without liver/biliary disease, or SALI with CLD). We identified if an ICD-9-CM or CPT code (listed in Appendix I) for a liver biopsy was recorded 182 days before or after the principal hospital SALI diagnosis code. We also collected External-Cause-of-Injury codes, or E-codes, associated with a SALI diagnosis. E-codes are a subset of ICD-9-CM codes that could permit the classification of environmental events, circumstances, and conditions as the cause of an adverse effect.[25] Information was collected on the presence and position of these codes, as well as the SALI codes of interest (Table 1). The collection of these electronic data allowed for the PPV determination of ICD-9-CM codes and code combinations including liver biopsy and/or E-codes, as well as several secondary analyses (describes in detail in Section III.G).

D. CHART ABSTRACTION

Two trained abstractors reviewed the redacted medical records of all potential cases. Data were abstracted onto an electronic version of a structured form (Appendix J) using a Research Electronic Data Capture (REDCap) database, an electronic data capture tool hosted at the University of Pennsylvania. REDCap is a secure, web-based application designed to support data capture by providing: 1) an intuitive interface for validated data entry; 2) audit trails for tracking data manipulation and export procedures; 3) automated export procedures for seamless data downloads to common statistical packages; and 4) procedures for importing data from external sources.[28] The abstraction form collected information from laboratory results, admission history and physical examinations, physician progress notes, hospital discharge summaries, brain imaging reports, and liver biopsy reports. Details of specific data variables collected are shown in Table 2.

Table 2. Data collected from hospital medical records to permit determination of severe acute liver injury (SALI) and acute liver failure.

Laboratory Results	Physician Progress Notes	Brain Imaging Reports+
Alanine aminotransferase*	Diagnoses of:	Diagnoses of:
Alkaline phosphatase*	**1.** Acute (or fulminant) hepatitis (or liver injury)	**1.** Acute cerebral ischemia
Alpha-fetoprotein	**2.** Asterixis†	**2.** Acute stroke
Ammonia*	**3.** Acute (or fulminant) liver failure	**3.** Cerebral edema
Anti-kidney liver microsomal type 1 Ab	**4.** Hepatic encephalopathy‡	**4.** Intracranial/cerebral bleed
Anti-mitochondrial Ab	**5.** Jaundice	**5.** Intracranial/cerebral mass
Anti-nuclear Ab	Drugs to treat encephalopathyΨ	**6.** Uncal herniation
Anti-smooth muscle Ab	Liver transplantation	
Aspartate aminotransferase*	Pre-existing liver disease	
Ceruloplasmin	Suspected SALI etiology	
Cytomegalovirus IgG Ab	Use of argatroban, warfarin	
Ethanol	Use of mechanical ventilation	
Gamma-glutamyl transpeptidase*		
Hepatitis A IgM, IgG Ab	**Admission History/Exam and Hospital Discharge Summaries**	
Hepatitis B core IgM Ab		
Hepatitis B surface antigen	Diagnoses of:	
Hepatitis C Ab	**1.** Acute (or fulminant) hepatitis (or liver injury)	
Hepatitis C RNA	**2.** Asterixis†	
Hepatitis D Ab	**3.** Acute (or fulminant) liver failure	
Hepatitis E Ab	**4.** Jaundice	
International normalize ratio*	**5.** Hepatic encephalopathy‡	
Total bilirubin*	Pre-existing liver disease	
	Suspected SALI etiology	

Ab=antibody

* Admission and peak results

‡ Hepatic encephalopathy was recorded if there was a report of altered mentation and a diagnosis was recorded in a physician's note.

† Asterixis was recorded if documented in a physician's physical examination.

Ψ Drugs to treat hepatic encephalopathy included: lactulose, flumazenil, intravenous mannitol, methylprednisolone, pentobarbital, rifaximin, and thiopental.

+ Reports from computed tomography and magnetic resonance imaging studies of the brain.

E. CASE ADJUDICATION

After medical record review, data abstraction forms and redacted records were independently reviewed by two hepatologists, who served as endpoints adjudicators. Using an electronic version of a structured form (Appendix K), they classified each SALI case as: 1) definite, 2) no event, or 3) unable to determine (for members with a missing ALT, AST, or total bilirubin result). Among members with a hospital discharge ICD-9-CM diagnosis indicative of ALF (Table 1), the adjudicators classified each ALF case as: 1) definite, 2) no event, or 3) unable to determine (for members with insufficient records). Disagreement on any classification resulted in review by a third hepatologist to adjudicate the event.

F. ELECTRONIC DATA AMONG MEMBERS WITH SALI DIAGNOSES IN THE MSDD

Across the eight member health plans of the five Data Partners, we identified all members that had an inpatient SALI diagnosis code in any position (i.e., principal and non-principal) between 2009 and 2010

and at least 12 months of prior continuous membership. For these members, we collected electronic data on: 1) the position of the SALI diagnosis codes of interest, 2) the presence and position of any E-codes that accompanied the SALI diagnosis, and 3) the presence of an ICD-9-CM or CPT code for liver biopsy recorded 182 days before or after the principal hospital SALI diagnosis code.

G. STATISTICAL ANALYSES

We sought to identify code-based algorithms separately in members without pre-existing liver/biliary disease and with CLD with a PPV exceeding 80% in administrative claims-based databases. Our focus was on PPV because a sufficiently high PPV provides confidence that identified outcomes are true events.

For members without a pre-existing liver/biliary disease, we determined the PPVs with 95% confidence intervals (CI) of each ICD-9-CM code and common code combinations for confirmed SALI. We examined if the addition of a liver biopsy or E-code increased PPVs. Further, among members with a diagnosis code suggestive of ALF (Table 1), we determined the PPVs of these codes and combinations for adjudicator-confirmed ALF. For members with a CLD diagnosis, we then determined the PPVs of the codes and common code combinations for confirmed SALI.

Finally, we conducted several secondary analyses among all members within the eight selected Data Partner health plans who had a hospital-associated SALI diagnosis code (Table 1) in any position between 2009 and 2010. First, we determined the frequency of each diagnosis code and frequent code combinations. Second, we determined the frequency with which these codes were accompanied by E-codes or liver biopsy claims. Finally, to explore the extent to which SALI events might be missed by evaluating only principal diagnoses, we determined the proportion that had a hospital SALI diagnosis in a non-principal compared to principal position among all eligible members in the participating Data Partner health plans. Results were stratified by CLD status.

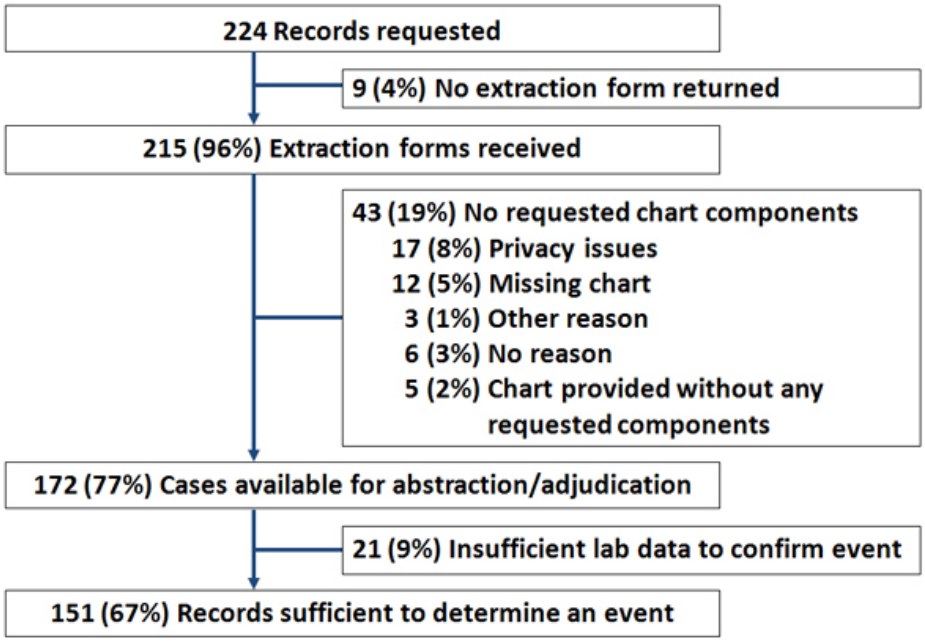
We estimated that 75 members would allow determination of the PPV of the diagnostic codes and laboratory abnormalities with a maximum 95% CI of ±0.11, assuming a PPV of 80%. Data were analyzed using Stata 12.0 (Stata Corp, College Station, TX).

IV. RESULTS

A. CASE RETRIEVAL RESULTS

A summary of the case retrieval results can be found in Figure 1 and is described in the sections below.

Figure 1. Flow chart of overall case retrieval results. All percentages are based on the number of records requested.



1. Responses to chart requests

Of the 224 charts requested, Data Partners were able to identify and return a completed extraction form for 215 (96.0%) cases. No extraction forms were received for nine (4.0%) of the chart requests (Table 3, shaded cells). DP8 submitted an extra CLD chart from their listing of identified members with potential SALI events in response to another Data Partner not being able to obtain all of the CLD charts requested. This site was able to identify an additional chart and had the budget to retrieve, redact, and submit it.

Table 3. Number of charts requested and responses received by each Data Partner health plan.

	No Pre-Existing Liver or Biliary Disease		Chronic Liver Disease		
Data Partner Health Plan	Charts Requested	Responses Received‡	Charts Requested	Responses Received‡	Total Responses Received
DP1	30	30	20	20	50
DP2	30	29	20	13	42
DP3	6	6	5	5	11
DP4	30	30	15	15	45
DP5	12	12	2	2	14
DP6	14	14	5	5	19
DP7	13	11	3	3	14
DP8	14	14	5	6	20
Total	149	146	75	69	215

* Shaded cells denote Data Partner health plans that did not return extraction forms for all chart requests.
‡ Refers to the return of a completed extraction form from the Data Partner.

2. Proportion of requested chart components provided

Of the 224 potential cases identified, the requested chart components were not provided for 43 (19.2%). Of those, charts for 17 (7.6%) cases were not obtained because of authorization or privacy issues (i.e., IRB restricted chart retrieval, provider required member authorization); twelve charts (5.4%) were missing or not found; two (0.9%) charts were not obtained because the date of service indicated was not a hospitalization; in one (0.4%) case, the provider refused to participate; a reason was not indicated for six (2.7%) cases; and for five (2.2%) cases, redacted chart information was provided, but none of the requested chart components were included (the reason for this was not collected). Therefore, a total of 172 (76.8%) cases had the requested chart components provided.

The number of charts not provided and the reasons they could not be obtained varied widely by Data Partner health plan (Table 4). Four of the Data Partner health plans were unable to obtain any requested chart components for more than 20% of the cases.

Table 4. Reasons requested chart components were not provided by Data Partner health plan.

Data Partner Health Plan	No. of Charts Requested	No. with Privacy Issues	No. with Missing Chart	No. with Other Reason	No. with No Reason Provided	Charts Provided without Requested Components	Total (% of Requested Charts)
DP1	50	0	0	0	2	0	2 (4.0%)
DP2	50	2	0	0	4	5	11 (22.0%)
DP3	11	0	0	0	0	0	0 (0%)
DP4	45	7	6	1	0	0	14 (31.1%)
DP5	14	2	0	0	0	0	2 (14.3%)
DP6	19	5	0	2	0	0	7 (36.8%)
DP7	16	1	0	0	0	0	1 (6.3%)
DP8	19	0	6	0	0	0	6 (31.6%)
Total	224	17	12	3	6	5	43 (19.2%)

3. Charts with insufficient laboratory data to confirm an event

For a total of 21 (9.4%) cases, the requested chart components were provided but did not have sufficient laboratory records available to confirm an event, as indicated by both adjudicators. This was evenly distributed across the Data Partner health plans (Table 5).

Table 5. Number of insufficient records provided by Data Partner health plan.

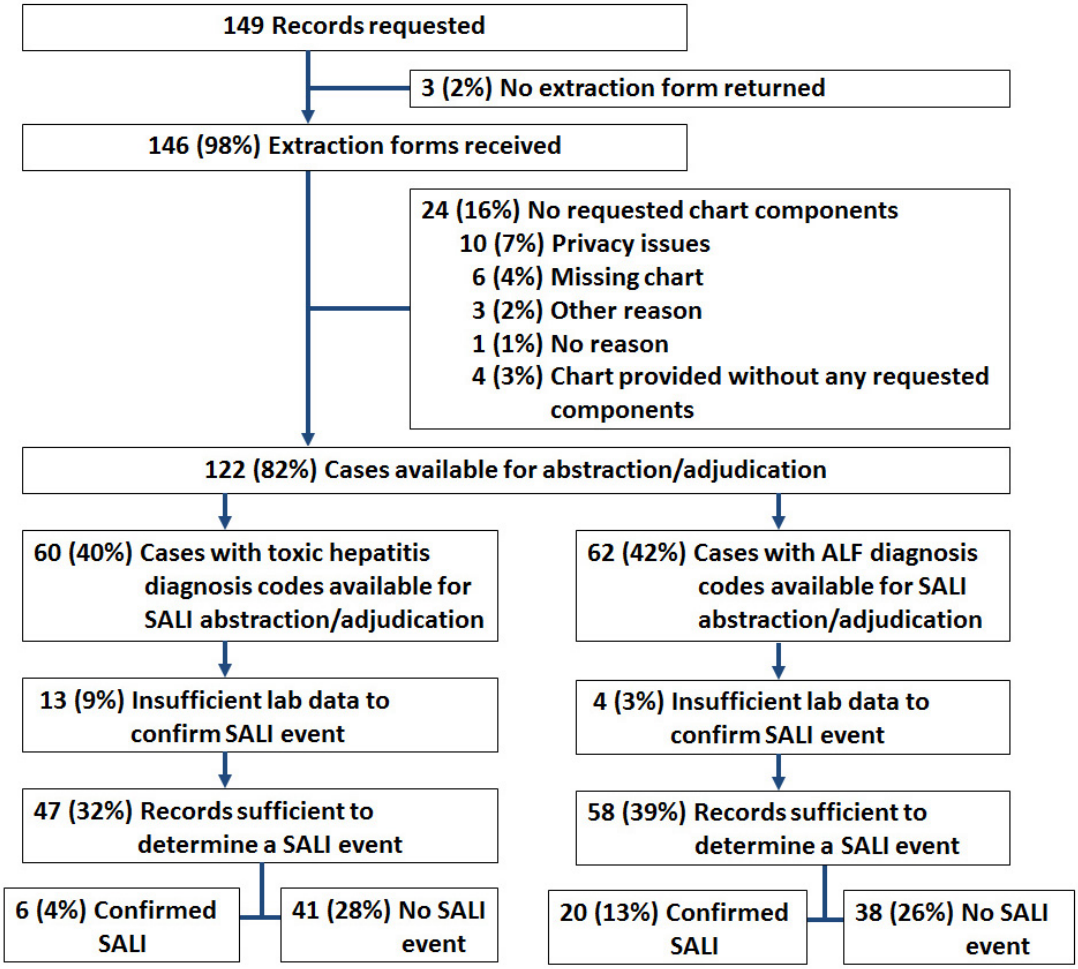
Data Partner Health Plan	No. of Responses	No. Insufficient (% of Responses Received)
DP1	50	5 (10.0%)
DP2	42	6 (14.3%)
DP3	11	0 (0%)
DP4	45	1 (2.2%)
DP5	14	4(28.6%)
DP6	19	2 (10.5%)
DP7	14	1 (7.1%)
DP8	20	2 (10.0%)
Total	215	21 (9.8%)

B. VALIDITY OF SALI DIAGNOSES IN MEMBERS WITHOUT LIVER/BILIARY DISEASE

1. Chart retrieval results

Among the 149 randomly sampled members who had a principal hospital SALI diagnosis and no pre-existing liver/biliary disease, extraction forms were not received for 3 (2.0%) cases, and 24 (16.1%) cases did not have any requested chart components provided (see Figure 2 for reasons). Thus, medical records from 122 (81.9%) members were therefore available for abstraction.

Figure 2. Flow chart of case retrieval results and severe acute liver injury (SALI) event confirmation for health plan members without liver/biliary disease. All percentages are based on the number of records requested.



2. Characteristics of sample

The median age of these 122 members was 68 years (interquartile range [IQR], 50-80; range, 12-94), and 78 (63.9%) were female. Of the 122 cases, a total of 19 (15.6%) had a liver biopsy claim recorded within 182 days before or after the hospital SALI diagnosis. Further, six (4.9%) members had an E-code accompanying the SALI diagnosis. Among the 60 members with toxic hepatitis diagnosis codes, the median age was 69 years (interquartile range [IQR], 52-81; range, 12-92), and 47 (78.3%) were female. Of these 60 cases, a total of 14 (23.3%) had a liver biopsy claim recorded within 182 days before or after

the hospital SALI diagnosis. Further, 3 (5.0%) members had an E-code accompanying the SALI diagnosis. Among the 62 members with ALF diagnosis codes, the median age was 64 years (interquartile range [IQR], 49-75; range, 12-94), and 31 (50.0%) were female. Of these 62 cases, a total of 5 (8.1%) had a liver biopsy claim recorded within 182 days before or after the hospital SALI diagnosis. Further, 3 (5.0%) members had an E-code accompanying the SALI diagnosis.

3. Confirmation of SALI events

Among the 122 members with available chart components, the adjudicators determined that 17/122 (13.9%) did not have sufficient laboratory records available to permit confirmation of SALI (Figure 2). After adjudication, 26 (24.8%; 95% CI, 16.9%-34.1%) of the 105 cases with a diagnostic code of interest and sufficient data were confirmed to have SALI. The overall percent agreement in events between the two adjudicators was 83.6% (102/122; 95% CI, 75.8%-89.7%), and the kappa was 0.69.

Confirmed cases of SALI (n=26) had a median of one SALI diagnosis code recorded, and those without chart-confirmed SALI (n=79) also had a median of one code present. True and false positive case numbers for individual ICD-9-CM codes and code combination were used to determine PPVs. The PPVs of individual ICD-9-CM codes of interest and combinations of these codes for confirmed SALI are listed in Table 6. The PPVs of the individual ICD-9-CM codes for confirmed SALI were generally low, ranging from 6.5% to 54.3%.

Table 6. Positive predictive values (with 95% confidence intervals) of hospital International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes and combinations for adjudicated cases of severe acute liver injury (SALI) among 105 health plan members without pre-existing liver/biliary disease.

ICD-9-CM Code or Combination		No. with Code(s)*	No. with SALI	Positive Predictive Value (95% Confidence Interval)
Any SALI code		105	26	24.8% (16.9% - 34.1%)
573.3	Toxic hepatitis	26	11	42.3% (23.4% - 63.1%)
573.8	Other liver disorder	31	2	6.5% (0.8% - 21.4%)
570	Acute/subacute hepatic necrosis	35	19	54.3% (36.7% - 71.2%)
572.2	Hepatic coma	23	3	13.0% (2.8% - 33.6%)
572.4	Hepatorenal syndrome	0	0	-
572.8	Liver disease sequelae	13	7	53.8% (25.1% - 80.8%)
V42.7	Liver transplant	0	0	-
573.3 + 570	Toxic hepatitis + hepatic necrosis	10	6	60.0% (26.2% - 87.8%)
573.3 or 570‡	Toxic hepatitis or hepatic necrosis	51	24	47.1% (32.9% - 61.5%)
573.3 + 572.2	Toxic hepatitis + hepatic coma	1	1	100% (2.5% - 100%)
573.3 + 572.8	Toxic hepatitis + liver disease sequelae	2	2	100% (15.8% - 100%)
573.8 + 570	Other liver disorder + hepatic necrosis	1	1	100% (2.5% - 100%)
573.8 + 572.2	Other liver disorder + hepatic coma	0	0	-
573.8 + 572.8	Other liver disorder + liver disease sequelae	0	0	-
570 + 572.2	Hepatic necrosis + hepatic coma	3	2	66.6% (9.4% - 99.2%)
570 + 572.8	Hepatic necrosis + liver disease sequelae	7	7	100% (59.0% - 100%)
573.3 + liver biopsy code	Toxic hepatitis + liver biopsy	4	3	75.0% (19.4% - 99.4%)
573.8 + liver biopsy code	Other liver disorder + liver biopsy	6	1	16.7% (0.4% - 64.1%)
570 + liver biopsy code	Hepatic necrosis + liver biopsy	4	3	75.0% (19.4% - 99.4%)
572.8 + liver biopsy code	Liver disease sequelae + liver biopsy	1	1	100% (2.5% - 100%)
Any SALI code + liver biopsy		14	6	42.9% (17.7% - 71.1%)
Any SALI code + any E-code		6	2	33.3% (4.33% - 77.72%
Any Two SALI codes		19	12	63.2% (38.4% - 83.7%)
570 + any other SALI code		17	12	70.6% (44.0% - 89.7%)
573.3 + any other SALI code		10	6	60.0% (26.2% - 87.8%)
572.8 + any other SALI code		9	7	77.8% (40.0% - 97.2%)

* This table includes codes from any position; therefore, more than one code may have been applied to a single member.
‡ Refers to members who had either ICD-9-CM code 573.3 or 570 recorded.

In contrast, the presence of a hospitalization containing the combination of diagnosis codes for both acute hepatic necrosis (570) plus liver disease sequelae (572.8) (i.e., either one principal and one secondary or two secondary diagnoses) had high PPV (100%; 95% CI, 59.0% – 100%) and captured the highest proportion of cases (7/26 [26.9%]) among the diagnostic coding algorithms evaluated (**Table 6**). In addition to the prior coding algorithm, a hospital diagnosis of toxic hepatitis (573.3) plus either hepatic coma (572.2) or liver disease sequelae (572.8), as well as a hospital diagnosis of acute hepatic necrosis (570) plus other specified liver disorders (573.8) both had PPVs of 100% (**Table 6**), but these algorithms identified few SALI cases.

Table 7 provides a list of the diseases observed among the 79 members who were adjudicated as not having had severe acute liver injury, according to diagnosis code. The majority of these members were observed upon adjudication to have had a liver cyst (20.3%), normal liver-related laboratory tests with

no documented hepatic abnormality (18.9%), or alcoholic liver disease that did not meet severe acute liver injury criteria (10.1%) (Table 7).

Table 7. Conditions observed among 79 health plan members without pre-existing liver/biliary disease who were adjudicated as not having had severe acute liver injury, by primary International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) code.

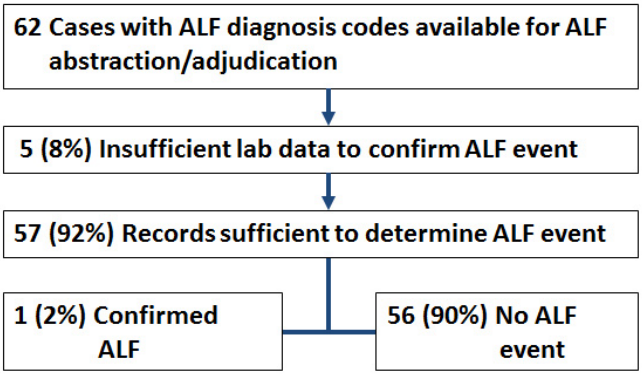
ICD-9-CM Code	Code Description	No. with Primary Code	Condition
570	Acute and subacute necrosis of liver	15	n=5, Drug-induced liver injury, not meeting severe acute liver injury criteria n=3, Abnormal liver-related laboratory tests of unclear etiology n=2, Alcoholic liver disease n=2, Cancer in the liver n=1, Ischemic hepatopathy n=1, Normal liver-related laboratory tests with no reported hepatic abnormality n=1, Systemic infection with abnormal liver-related laboratory tests
572.2	Hepatic coma	19*	n=6, Alcoholic liver disease with altered mental status n=5, Chronic liver disease-induced cirrhosis, with hepatic encephalopathy n=4, Toxic/metabolic encephalopathy n=2, Normal liver-related laboratory tests with altered mental status and no reported hepatic abnormality n=1, Normal liver-related laboratory tests and no reported altered mental status or hepatic abnormality n=1, Systemic infection with altered mental status and abnormal liver-related laboratory tests
572.4	Hepatorenal syndrome	0	
572.8	Sequelae of liver disease	5*	n=2, Normal liver-related laboratory tests with no reported hepatic abnormality n=1, Alcoholic liver disease n=1, Hepatic cyst n=1, Systemic infection with abnormal liver-related laboratory tests
573.3	Toxic (non-infectious) hepatitis	12	n=3, Cholelithiasis n=3, Systemic infection with abnormal liver-related laboratory tests n=2, Abnormal liver-related laboratory test of unclear etiology n=2, Drug-induced liver injury, not meeting severe acute liver injury criteria n=1, Normal liver-related laboratory tests with no reported hepatic abnormality n=1, Ischemic hepatopathy
573.8	Other specified liver disorder	29	n=15, Hepatic cyst n=5, Hemangioma n=4, Normal liver-related laboratory tests with no reported hepatic abnormality n=2, Cancer in the liver n=2, Ischemic hepatopathy n=1, Hepatic fluid collection
V42.7	Liver transplant	0	

* One member had both a primary ICD-9-CM 572.2 and 572.8.

4. Confirmation of ALF events

Among 57 members with a principal hospital diagnosis code suggestive of ALF and available chart components to permit adjudication of the outcome, one (1.8%; 95% CI, 0.04% - 9.4%) case was confirmed to be consistent with a diagnosis of ALF (Figure 3). Both adjudicators agreed that this case had an ALF event. There were no confirmed ALF events among members with a principal hospital diagnosis code suggestive of toxic hepatitis.

Figure 3. Flow chart of acute liver failure (ALF) event confirmation for health plan members without liver/biliary disease.



The PPVs of the ICD-9-CM codes and code combinations for confirmed ALF are shown in Table 8. The PPVs for individual ICD-9-CM codes and code combinations for confirmed ALF were all very low (range, 1.8% - 1.9%).

Table 8. Positive predictive values (with 95% confidence intervals) of hospital International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes and combinations for adjudicated cases of acute liver failure (ALF) among 57 health plan members without pre-existing liver/biliary disease.

ICD-9-CM Code or Combination		No. with Code(s)*	No. with ALF	Positive Predictive Value (95% Confidence Interval)
Any acute liver failure code		57	1	1.8% (0.04% - 9.4%)
570	Acute/subacute hepatic necrosis	33	1	3.0% (0.08% - 15.8%)
572.2	Hepatic coma	22	1	4.6% (0.12% - 22.8%)
572.4	Hepatorenal syndrome	0	0	-
572.8	Liver disease sequelae	11	1	9.1% (0.2% - 41.3%)
V42.7	Liver transplant	0	0	-
Any acute liver failure code + biopsy		5	1	20.0% (0.5% - 71.6%)
Any acute liver failure code + E-code		3	0	0%

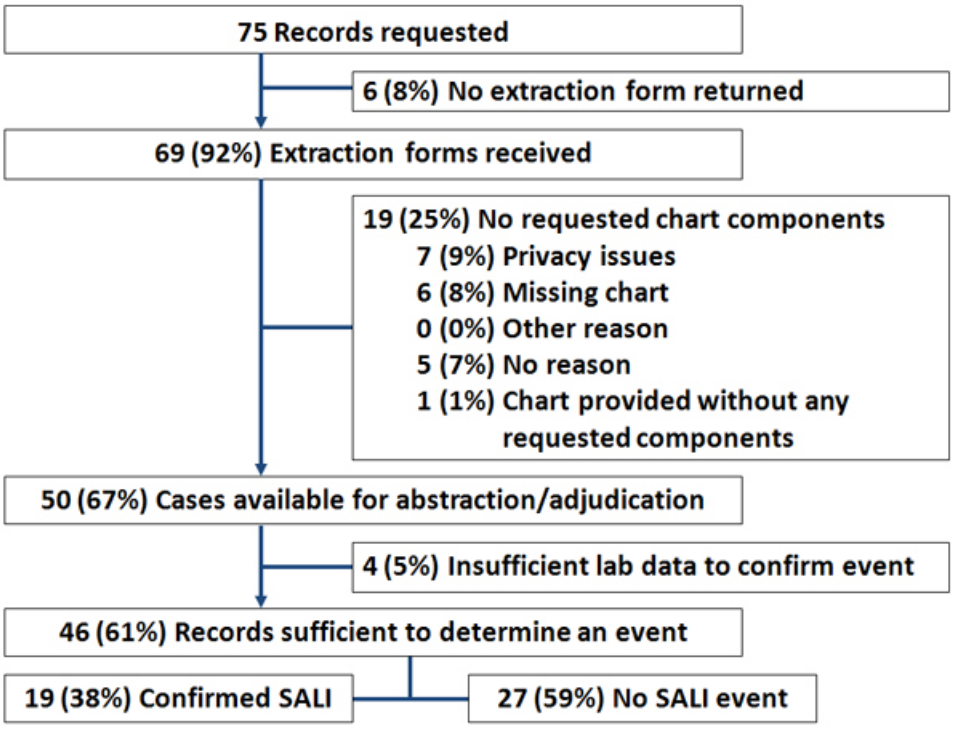
* This table includes acute liver failure ICD-9-CM codes from any position. Therefore, more than one code may have been applied to a single member.

C. VALIDITY OF SALI DIAGNOSES IN MEMBERS WITH PRE-EXISTING CHRONIC LIVER DISEASE

1. Chart retrieval results

Among the 75 randomly sampled members with pre-existing CLD and a principal inpatient SALI diagnosis, extraction forms were not received for 6 (8.0%) cases and 19 (25.3%) cases did not have any requested chart components provided (see Figure 4 for reasons). Medical records from 50 (66.7%) members were therefore available for abstraction.

Figure 4. Flow chart of case retrieval results for health plan members with chronic liver disease. All percentages are based on the number of records requested.



2. Characteristics of sample

The median age of these 50 members was 56 years (IQR, 46-64; range, 28-85), and 20 (40.0%) were female. Of the 50 cases, only four (8.0%) of these cases had an accompanying liver biopsy code and one (2.0%) had an E-code recorded with the SALI diagnosis.

3. Confirmation of SALI events

Among the 50 members with available chart components, the adjudicators determined that 4 (8.0%) did not have sufficient laboratory records available to permit confirmation of SALI (Figure 4). After adjudication, 19 (38.0%; 95% CI, 27.0% - 56.8%) of these 46 cases were confirmed to have SALI. The overall percent agreement in SALI events between the two adjudicators was 94.0% (47/50; 95% CI, 83.5%-98.7%), and the kappa was 0.38.

Confirmed cases of SALI had a median of two SALI diagnosis codes recorded, and those without chart-confirmed SALI had a median of one code present. The PPVs of ICD-9-CM codes and combinations for confirmed SALI for these members are listed in Table 9. The PPVs of the individual ICD-9-CM codes for confirmed SALI among CLD members were higher in magnitude than for those without pre-existing liver/biliary disease, but only the diagnosis code for hepatorenal syndrome (572.4), accompanying 4/19 cases that were adjudicated as SALI, had a high PPV (4/4; PPV, 100%; 95% CI, 39.8% - 100%).

Table 9. Positive predictive values (with 95% confidence intervals) of hospital International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes and combinations for adjudicated cases of severe acute liver injury (SALI) among 46 health plan members with chronic liver disease.

ICD-9-CM Code or Combination		No. with Code(s)*	No. with SALI	Positive Predictive Value (95% Confidence Interval)
Any SALI code		46	19	41.3% (27.0% - 56.8%)
573.3	Toxic hepatitis	6	4	66.7% (22.3% - 95.7%)
573.8	Other liver disorder	6	2	33.3% (4.3% - 77.7%)
570	Acute/subacute hepatic necrosis	9	7	77.8% (40.0% - 97.2%)
572.2	Hepatic coma	33	14	42.4% (25.5% - 60.8%)
572.4	Hepatorenal syndrome	4	4	100% (39.8% - 100%)
572.8	Liver disease sequelae	15	9	60.0% (32.3% - 83.7%)
V42.7	Liver transplant	3	1	33.3% (0.8% - 90.6%)
573.3 + 570	Toxic hepatitis + hepatic necrosis	0	0	-
573.3 + 572.2	Toxic hepatitis + hepatic coma	4	3	75.0% (19.4% - 99.4%)
573.3 + 572.4	Toxic hepatitis + hepatorenal syndrome	0	0	-
573.3 + 572.8	Toxic hepatitis + liver disease sequelae	2	1	50.0% (1.3% - 98.7%)
573.3 + V42.7	Toxic hepatitis + liver transplant	0	0	-
573.8 + 570	Other liver disorder + hepatic necrosis	1	1	100% (2.5% - 100%)
573.8 + 572.2	Other liver disorder + hepatic coma	2	2	100% (15.8% - 100%)
573.8 + 572.4	Other liver disorder + hepatorenal syndrome	1	1	100% (2.5% - 100%)
573.8 + 572.8	Other liver disorder + liver disease sequelae	2	2	100% (15.8% - 100%)
573.8 + V42.7	Other liver disorder + liver transplant	2	1	50.0% (1.3% - 98.7%)
570 + 572.2	Hepatic necrosis + hepatic coma	5	4	80.0% (28.4% - 99.5%)
570 + 572.4	Hepatic necrosis + hepatorenal syndrome	1	1	100% (2.5% - 100%)
570 + 572.8	Hepatic necrosis + liver disease sequelae	5	5	100% (47.8% - 100%)
570 + V42.7	Hepatic necrosis + liver transplant	1	1	100% (2.5% - 100%)
573.3 + liver biopsy code	Toxic hepatitis + liver biopsy	0	0	-
573.8 + liver biopsy code	Other liver disorder + liver biopsy	1	0	0% (0.0% - 97.5%)
570 + liver biopsy code	Hepatic necrosis + liver biopsy	1	1	100% (2.5% - 100%)
572.8 + liver biopsy code	Liver disease sequelae + liver biopsy	1	0	0% (0.0% - 97.5%)
Any SALI code + liver biopsy		3	1	33.3% (0.8% - 90.6%)
Any SALI code + any E-code		1	0	0% (0.0% - 97.5%)
Any Two SALI codes		18	12	66.7% (41.0% - 86.7%)
570 + any other SALI code		6	5	83.3% (35.9% - 99.6%)
572.8 + any other SALI code		13	9	69.2% (38.6% - 90.9%)
573.3 + any other SALI code		4	3	75.0% (19.4% - 99.4%)
573.8 + any other SALI code		3	2	66.7% (9.4% - 100.0%)
(570 or 573.3) + any other SALI code		10	8	80.0% (44.4% - 97.5%)
(570 or 572.4) + any other SALI code		12	10	83.3% (51.6% - 97.9%)

* This table includes codes from any position; therefore, more than one code may have been applied to a single member.

The combination of a hospital diagnosis of either acute hepatic necrosis (570) or hepatorenal syndrome (572.4) plus any other SALI code had a PPV of 83.3% (95% CI, 51.6% – 97.9%) and identified the highest proportion of cases (10/19 [52.6%]). Several other SALI code combination algorithms evaluated in **Table 9** also had PPVs exceeding 80%, but these algorithms identified fewer SALI cases.

Table 10 provides a list of the diseases observed among the 27 members with CLD who were adjudicated as not having had severe acute liver injury. The majority of members were observed upon adjudication to have had hepatic encephalopathy with abnormal liver-related laboratory tests that did not meet SALI criteria (16/27; 59.3%) and abnormal liver-related laboratory test of unclear etiology that did not meet SALI criteria (6/27; 22.2%).

Table 10. Conditions observed among 27 chronic liver disease health plan members who were adjudicated as not having had severe acute liver injury, by primary International Classification of Disease, Ninth Revision, Clinical Modification (ICD-9-CM) code.

ICD-9-CM Code	Code Description	No. With Primary Code	Condition
570	Acute and subacute necrosis of liver	1	n=1, Hepatic encephalopathy with abnormal liver-related laboratory tests
572.2	Hepatic coma	19	n=15, Hepatic encephalopathy with abnormal liver-related laboratory tests n=3, Abnormal liver-related laboratory test of unclear etiology n=1, Alcoholic liver disease
572.4	Hepatorenal syndrome	0	
572.8	Sequelae of liver disease	2	n=1, Systemic infection with abnormal liver-related laboratory tests n=1, Drug hypersensitivity reaction, normal liver-related laboratory tests
573.3	Toxic (non-infectious) hepatitis	1	n=1, Abnormal liver-related laboratory test of unclear etiology
573.8	Other specified liver disorder	4	n=2, Abnormal liver-related laboratory test of unclear etiology n=2, Cancer in the liver
V42.7	Liver transplant	0	

D. ANALYSIS OF SALI DIAGNOSES IN THE MSDD

Across the eight participating Data Partner health plans within the MSDD, there were 55,334,046 members with at least 12 months of continuous enrollment between 2009 and 2010. Among these members, 28,321 (0.05%) had a hospital-associated SALI ICD-9-CM diagnosis code recorded in either a principal or non-principal position. The frequencies of each diagnosis code and common code combinations are presented in Table 11 and Table 12. The most frequently recorded SALI hospital diagnosis codes among members without pre-existing liver/biliary disease were other specified liver disorders (573.8; 55.2%), acute hepatic necrosis (570; 21.7%), and toxic hepatitis (573.3; 18.8%). The most commonly recorded hospital diagnosis code combination was toxic hepatitis (573.3) with acute hepatic necrosis (570). The most frequently recorded SALI hospital diagnosis codes among CLD cases were hepatic coma (572.2; 28.2%), liver transplantation (V42.7; 25.0%), and toxic hepatitis (573.3; 21.3%). The most commonly recorded hospital diagnosis code combination among CLD cases was toxic hepatitis (573.3) with acute hepatic necrosis (570).

Among the 28,321 members with a hospital-associated SALI ICD-9-CM diagnosis code in any position, 8,324 (29.4%) had a claim for a liver biopsy within 182 days of the hospital SALI diagnosis. Members with CLD were more likely to have had a claim for a liver biopsy than those without pre-existing liver/biliary disease (506/1,020 [49.6%] versus 7,818/27,301 [28.6%]; p<0.001). Further, among these 28,321 cases, 363 (1.3%) had an E-code recorded with the SALI diagnosis. The most commonly recorded E-codes were E935 (analgesics, antipyretics, and anti-rheumatics; 0.18%), E934 (agents primarily affecting blood constituents; 0.17%), and E933 (systemic agents; 0.16%). No difference was observed in the prevalence of an E-code between members without pre-existing liver/biliary disease and those with CLD (352 [1.3%] versus 11 [1.1%]; p=0.67).

Among the 28,321 members with a hospital-associated SALI ICD-9-CM diagnosis code in any position, 2,249 (7.9%) had the code recorded in a principal position. Those with CLD were more likely to have the code recorded in a principal position than those without pre-existing liver/biliary disease (113/1,020 [11.1%] versus 2,136/27,301 [7.8%], p<0.001).

Table 11. Frequency and extent of overlap of hospital International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes, in any position, suggestive of severe acute liver injury (SALI) among members without pre-existing liver/biliary disease across the eight participating Data Partner health plans.

ICD-9-CM Code or Combination		Frequency
Any SALI code		27,301 (100%)
573.3	Toxic hepatitis	5,142 (18.8%)
573.8	Other liver disorder	15,058 (55.2%)
570	Acute/subacute hepatic necrosis	5,920 (21.7%)
572.2	Hepatic coma	1,751 (6.4%)
572.4	Hepatorenal syndrome	296 (1.1%)
572.8	Liver disease sequelae	1,384 (5.1%)
V42.7	Liver transplant	636 (2.3%)
573.3 + 570	Toxic hepatitis + hepatic necrosis	845 (3.1%)
573.3 + 572.2	Toxic hepatitis + hepatic coma	142 (0.5%)
573.3 + 572.4	Toxic hepatitis + hepatorenal syndrome	33 (0.1%)
573.3 + 572.8	Toxic hepatitis + liver disease sequelae	205 (0.8%)
573.3 + V42.7	Toxic hepatitis + liver transplant	20 (0.1%)
573.8 + 570	Other liver disorder + hepatic necrosis	366 (1.3%)
573.8 + 572.2	Other liver disorder + hepatic coma	116 (0.4%)
573.8 + 572.4	Other liver disorder + hepatorenal syndrome	39 (0.1%)
573.8 + 572.8	Other liver disorder + liver disease sequelae	160 (0.6%)
573.8 + V42.7	Other liver disorder + liver transplant	18 (0.1%)
570 + 572.2	Hepatic necrosis + hepatic coma	309 (1.1%)
570 + 572.8	Hepatic necrosis + liver disease sequelae	480 (1.8%)
570 + V42.7	Hepatic necrosis + liver transplant	36 (0.1%)
Any SALI code + any E-code		352 (1.3%)
Any Two SALI codes		2,264 (8.3%)
570 + any other SALI code		1,575 (5.8%)
573.3 + any other SALI code		1,238 (4.5%)
572.8 + any other SALI code		748 (2.7%)

Table 12. Frequency and extent of overlap of hospital International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes, in any position, suggestive of severe acute liver injury (SALI) among members with chronic liver disease across the eight participating Data Partner health plans.

ICD-9-CM Code or Combination		Frequency
Any SALI code		1,020 (100%)
573.3	Toxic hepatitis	217 (21.3%)
573.8	Other liver disorder	178 (17.5%)
570	Acute/subacute hepatic necrosis	108 (10.6%)
572.2	Hepatic coma	288 (28.2%)
572.4	Hepatorenal syndrome	37 (3.6%)
572.8	Liver disease sequelae	138 (13.5%)
V42.7	Liver transplant	255 (25.0%)
573.3 + 570	Toxic hepatitis + hepatic necrosis	308 (30.2%)
573.3 + 570	Toxic hepatitis + hepatic necrosis	17 (1.7%)
573.3 + 572.2	Toxic hepatitis + hepatic coma	16 (1.6%)
573.3 + 572.4	Toxic hepatitis + hepatorenal syndrome	1 (0.1%)
573.3 + 572.8	Toxic hepatitis + liver disease sequelae	5 (0.5%)
573.3 + V42.7	Toxic hepatitis + liver transplant	7 (0.7%)
573.8 + 570	Other liver disorder + hepatic necrosis	9 (0.9%)
573.8 + 572.2	Other liver disorder + hepatic coma	15 (1.5%)
573.8 + 572.4	Other liver disorder + hepatorenal syndrome	4 (0.4%)
573.8 + 572.8	Other liver disorder + liver disease sequelae	10 (1.0%)
573.8 + V42.7	Other liver disorder + liver transplant	5 (0.5%)
570 + 572.2	Hepatic necrosis + hepatic coma	26 (2.6%)
570 + 572.8	Hepatic necrosis + liver disease sequelae	27 (2.7%)
570 + V42.7	Hepatic necrosis + liver transplant	7 (0.7%)
Any SALI code + any E-code		11 (1.1%)
Any Two SALI codes		152 (14.9%)
570 + any SALI code		58 (5.7%)
573.3 + any SALI code		39 (3.8%)
572.8 + any SALI code		81 (7.4%)

V. CONCLUSIONS AND LESSONS LEARNED

A. CONCLUSIONS

This project examined the ability of ICD-9-CM diagnostic codes and their combinations to identify cases of SALI in members without pre-existing liver/biliary disease and with pre-existing CLD in the MSDD. The individual pre-specified ICD-9-CM codes for identifying hospitalized SALI generally yielded low PPVs (24.7% for members without pre-existing liver/biliary disease; 41.3% for members with CLD). The ICD-9-CM codes for ALF also had low PPVs. For members without pre-existing liver/biliary disease, the presence of a hospital diagnosis of both acute hepatic necrosis (570) and liver disease sequelae (572.8) had high PPV (100%; 95% CI, 59.0% – 100%) and captured the highest proportion of events (26.9%) among the algorithms evaluated. For members with CLD, the combination of a hospital diagnosis of either acute hepatic necrosis (570) or hepatorenal syndrome (572.4) plus any other SALI code had a high PPV of 83.3% (95% CI, 51.6% - 97.9%) and identified the highest proportion of events (52.6%).

The PPVs of the individual SALI ICD-9-CM codes selected were low both for members without pre-existing liver/biliary disease and for those with CLD. In addition, the PPVs for the ALF ICD-9-CM codes were very low. This was likely due to the lack of specificity of the diagnostic codes and the overall low prevalence of ICD-9-CM diagnoses for both toxic hepatitis and ALF. In addition, the 95% CIs around these PPV estimates were wide because of the relatively small sample sizes of members with each code and with confirmed SALI.

Due to the observed low PPVs of the individual ICD-9-CM SALI codes, we examined coding algorithms that required the presence of combinations of SALI hospital ICD-9-CM codes. For members without pre-existing liver/biliary disease and with CLD, we identified coding algorithms that had PPVs exceeding 80%, though at the cost of missing confirmed cases identified by other codes. We believe that these algorithms require further validation because: 1) the PPVs were not determined using random samples of members with these specific combinations of codes, and 2) sample sizes of the subjects identified by these algorithms were small and insufficient to adequately determine their validity. If their validity is confirmed, future use of these coding algorithms will depend upon the specific research question. If the objective is to identify as many cases as possible (i.e., a sensitive diagnostic test), it may be advisable to utilize all of the SALI codes evaluated in these analyses to broadly screen cohorts of interest and then confirm these events using medical record review. Alternatively, if the aim is to reduce false positive events (i.e., a specific diagnostic test), the coding algorithms developed could be used without the need to confirm events via medical records, but this would be at the cost of missed events.

Very few studies have been performed to evaluate the accuracy of ICD-9-CM and ICD-10 diagnostic codes for SALI within administrative claims data. Myers and colleagues[7] evaluated the validity of these codes for ALF, defined by chart-confirmed encephalopathy and an INR ≥1.5, in the setting of acetaminophen overdose within the Calgary Health Region (now Alberta Health Services) in Canada. Their algorithm included codes for hepatic necrosis (570; K71.1), toxic hepatitis (573.3; K71.2, K71.6, K71.9), hepatic encephalopathy (572.2; K72.0, K72.9), hepatorenal syndrome (572.4; K76.7), jaundice (782.4; R17), coagulopathy (286.7; D68.4, D68.9), and adult respiratory distress syndrome (582.82; J80). Among 36 cases with an ICD-9-CM code of interest, 20 (PPV, 56%; 95% CI, 38% – 72%) had confirmed ALF. The accuracy of the algorithm was similar for ICD-9-CM and ICD-10 coding systems.

Jinjuvadia and colleagues[7] examined the utility of ICD-9-CM codes to identify members with drug-induced liver injury due to amoxicillin/clavulanic acid, phenytoin, valproic acid, and isoniazid within the University of Michigan Health System. Patients who were prescribed any of these drugs between 1994 and 2004 and who had a hospitalization with any of the following ICD-9-CM codes were identified: idiopathic jaundice (277.4); hepatic necrosis (570); liver disease sequelae (572.8); toxic hepatitis (573.3); jaundice, hepatocellular (573.8); cholestasis (576.8); and jaundice alone (782.4). Drug-induced liver injury was defined by a total bilirubin ≥2.5 mg/dL for isoniazid, phenytoin, and amoxicillin/clavulanic acid and a hospitalization with liver dysfunction (defined as INR ≥1.5, ALT >3 times ULN, and/or characteristic liver biopsy) for valproic acid. Among 7,395 members identified, 119 (1.6%) were confirmed to have had drug-induced liver injury. The PPVs of individual codes ranged from 0.4% – 3.0%. Coding algorithms were not developed and evaluated.

This project has several potential limitations. First, there is the potential that SALI events could have been misclassified during adjudication, particularly given the lower than expected kappa statistics and percent agreement in SALI events between the two adjudicators. However, we minimized this likelihood by: 1) using standardized definitions for SALI, 2) classifying events using a standard definition, and 3)

employing two endpoints adjudicators to confirm events, with a third to adjudicate cases in instances of disagreement. Second, each code-based algorithm missed some SALI events. Since the most severe strata of SALI, such as ALF, are especially rare, missing even a few of these events may be particularly problematic for future analyses evaluating such outcomes. Surveillance activities seeking to identify all possible SALI events should utilize all of the ICD-9-CM codes employed in these analyses to screen for potential events and then confirm endpoints by medical record review. Third, we did not determine the negative predictive value of the SALI codes, since we did not evaluate SALI among a sample of MSDD members without the SALI codes of interest. Fourth, the small number of confirmed SALI cases limited the precision of our PPV estimates. As a result, PPVs, particularly for the code combination algorithms, had very wide confidence intervals. Since we did not specifically obtain pre-specified sample sizes for each code combination algorithm, further evaluation of their PPV with sufficient numbers of members meeting the coding criteria should be considered. Finally, cases in these analyses were drawn from databases of mostly commercially-insured persons, potentially limiting the generalizability of our results to other populations. However, one of the selected Data Partners (Vanderbilt University School of Medicine/TennCare Bureau) includes members from the Tennessee Medicaid program.

This study had a number of strengths. We evaluated a number of ICD-9-CM codes suggestive of SALI and ALF. We classified both SALI and ALF events using standardized definitions and required two adjudicators to confirm outcomes, with a third arbitrating cases in instances of disagreement. Further, among members without SALI, we determined the etiology for their hospitalization to better understand which conditions the ICD-9-CM codes of interest were actually identifying. Finally, our use of the MSDD permitted our evaluation of the validity of the ICD-9-CM codes across a variety of administrative and claims-based data sources.

In conclusion, the individual pre-specified ICD-9-CM codes for identifying hospitalized SALI yielded generally low both for members without pre-existing liver/biliary disease and for members with CLD. The PPVs for ICD-9-CM codes suggestive of ALF were also very low. However, select combinations of SALI ICD-9-CM codes had high PPV for confirmed outcomes in both groups, but these algorithms missed some events. These algorithms could potentially be used within claims-based and electronic health record databases in future projects, after further validation, to examine the comparative risk of SALI associated with medical products of interest.

B. LESSONS LEARNED

1. Preparatory stages

During the initial 6-week development of the project proposal, the SALI workgroup worked without FDA collaboration. Future workgroups should consider collaborating with the FDA at project launch to improve efficiency.

2. Program code design

While the program code was designed to identify hospital diagnosis codes of interest, some identified cases were from services by other providers (i.e., pharmacies, physician's offices, etc.) instead of hospitalizations. For instance, there was one case where the index date identified was a regularly scheduled outpatient encounter followed by a hospitalization three weeks later. Future workgroups should consider and incorporate additional mechanisms to ensure that only hospitalizations are identified for chart retrieval if the primary goal is to identify hospitalized events. This would provide a

better chance of receiving comprehensive charts with the necessary information and would maximize efficiency during chart retrieval phase. Alternatively, after the initial run of the code by Data Partners, the workgroup could review a line list of identified claims to determine the comprehensiveness of the chart (i.e., location and provider of the data).

Additionally, Data Partners use varying naming schemes to identify their members. While these IDs must be used to identify a member within a Data Partner health plan, a more standardized naming system would be helpful for identified cases and charts. There were numerous instances where the ID number within the filename of redacted charts did not match the ID listed on the extraction form or the ID used in the MSDD and gathered by the program code. There was also no method in place to prevent Data Partners from using the same ID, so cases were assigned a unique identifier prior to chart abstraction. Therefore, the same case was identified by several IDs throughout the course of the project. Future workgroups should examine the possibility of having the program code assign a unique ID to identified cases, possibly containing a Data Partner flag, to ensure accuracy and improve efficiency.

3. Sufficient sample sizes

The algorithm and programming code had to be revised during the beta-testing phase due to insufficient sample sizes of SALI claims. When reasonable, workgroups should conduct a feasibility request during the early stages of the project to understand the counts and types of associated claims that may be available for the activity.

4. Extraction form design

The workgroup should ensure that the extraction form contains the minimum amount of fields to be completed by the Data Partner using chart information. If available, it is preferable to utilize electronic information pulled from the SAS program over information reported on the extraction form as this reduces time spent completing the form and the chance of transcription errors. Therefore, efforts should be made to limit the amount of duplicated information requested on the extraction form. Additionally, if there are numerous populations being identified (i.e. three different SALI groups), the extraction form should contain a field to report this information.

5. Preparation for chart retrieval

Before the start of chart retrieval, the workgroup should hold a call with all of the participating Data Partner health plans, including all of the staff completing the chart retrieval and data extraction process, to conduct a thorough walkthrough of the procedures. Sufficient instruction should be provided to Data Partners regarding any exceptions or special cases for redacting the standard set of HIPAA identifiers.

Workgroups should also create and provide Data Partners with documentation explaining how to retrieve charts based on the SAS program results (i.e., Data Partner programmers should create a crosswalk from the results to the identified chart to allow for extractors to locate the charts).

Additionally, workgroups should plan for seasonal variation in response time to chart requests (i.e. requesting charts over holidays) and allocate additional time to the chart retrieval phase as necessary.

6. Chart retrieval

Many charts contained additional chart components, sometimes comprising hundreds of pages, which were not requested. Sifting through these extraneous pages greatly increased the amount of time spent by the data abstractors and probably resulted in an increased burden by the Data Partners in pulling, copying, and redacting unnecessary pages of medical records.

In addition, the SALI workgroup had requested data on race be abstracted from medical records, but race was commonly found to be redacted, preventing its inclusion as a variable for analysis.

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VIII. APPENDICES

A. APPENDIX A. MEMBERS OF THE MINI-SENTINEL SEVERE ACUTE LIVER INJURY (SALI) VALIDATION WORKGROUP

Collaborator	Role
U.S. Food and Drug Administration	Provided input in protocol development, creation of SALI definitions, abstraction/adjudication forms development, validation of SALI endpoints, and interpretation of results.
Harvard Pilgrim Health Care Institute	**Mini-Sentinel Operations Center.** Provided administrative support and assistance; coordinated communication with Data Partners; coordinated chart retrieval process; provided Lead Site with de-identified data from Data Partners.
Perelman School of Medicine at the University of Pennsylvania	**Lead Site.** Designed project specifications; created all forms and manuals for the project; completed abstraction and adjudication; conducted data analyses; provided hepatologists for expert guidance.
HealthCore, Inc.	**Data Partners.** Implemented SAS program code for case selection; retrieved, copied, and de-identified specified chart components for selected cases; submitted data outputs and redacted charts to the Mini-Sentinel Operations Center.
Humana, Inc.	
Kaiser Permanente Center for Effectiveness and Safety Research: Kaiser Permanente Colorado – Institute for Health Research Kaiser Permanente Northwest	
HMO Research Network: Group Health Research Institute HealthPartners Institute for Education and Research Marshfield Clinic Research Foundation	
Vanderbilt University School of Medicine/TennCare Bureau	

B. APPENDIX B. LETTER TEMPLATE USED BY DATA PARTNERS FOR MEDICAL RECORD REQUESTS FROM PROVIDERS

Mini-Sentinel

<DATE>

<PROVIDER NAME>
<PROVIDER ADDRESS>

Re: Medical Records Request for FDA Medical Product Safety Monitoring System

We are contacting you regarding a project to facilitate the development of a fully operational medical product safety system for monitoring FDA-regulated medical products. <DATA PARTNER> is collaborating on this endeavor, Mini-Sentinel, with the Department of Population Medicine, Harvard Medical School/Harvard Pilgrim Health Care Institute, and the FDA.

This pilot has been designed in response to a Congressional mandate to monitor drug safety and your cooperation is key to successfully addressing this FDA priority public health initiative. In order to conduct this project, we require review of medical records for some of your patients hospitalized for severe acute liver injury.

We request that you: 1) allow us access to the relevant records for the attached list of patients; 2) obtain the relevant records for the attached list of patients and redact the individually identifiable health information and then send a copy of the record to us; or 3) send a copy of the record to VENDOR, a redaction service provider contracted by the Mini-Sentinel Coordinating Center, which will send the information to us after it has been redacted.

Enclosed are two letters from the FDA and Office of Human Research Protections identifying this as a priority public health surveillance activity that does not require authorization from you Institutional Review Board (IRB) or Privacy Board.

If you have any questions, please contact <NAME> at (###) ###-####. She/He is our leading research manager on this record review process and will be your key contact.

We greatly appreciate your time and assistance with this important public health initiative.

Sincerely,

NAME
TITLE

C. APPENDIX C. LIST OF INTERNATIONAL CLASSIFICATION OF DISEASES, NINTH REVISION, CLINICAL MODIFICATION (ICD-9-CM) CODES TO IDENTIFY PRE-EXISTING LIVER/BILIARY DISEASES.

CODE	DESCRIPTION
Hepatitis B	
070.20	VIRAL HEP B W/HEP COMA ACUTE/UNSPECIFIED W/O HEP DELTA
070.21	VIRAL HEP B W/HEP COMA ACUTE/UNSPEC W/HEP DELTA
070.30	VIRAL HEP B W/O HEP COMA ACUT/UNS W/O HEP DELTA
070.31	VIRAL HEP B W/O HEP COMA ACUT/UNS W/HEP DELTA
070.22	VIRAL HEP B W/HEP COMA CHRN W/O MENTION HEP DELTA
070.23	HEPATITIS B, CHRONIC, W HEPATIC COMA, W HEPATITIS DELTA
070.32	VIRAL HEP B W/O HEP COMA CHRN W/O HEP DELTA
070.33	VIRAL HEP B W/O MENTION HEP COMA CHRN W/HEP DELTA
V02.61	HEPATITIS B CARRIER
Hepatitis C	
070.41	ACUTE HEPATITIS C WITH HEPATIC COMA
070.51	ACUTE HEPATITIS C WITHOUT MENTION HEPATIC COMA
070.44	CHRONIC HEPATITIS C WITH HEPATIC COMA
070.54	CHRONIC HEPATITIS C WITHOUT MENTION HEPATIC COMA
070.70	UNSPECIFIED VIRAL HEPATITIS C W/O HEPATIC COMA
070.71	UNSPECIFIED VIRAL HEPATITIS C WITH HEPATIC COMA
V02.62	HEPATITIS C CARRIER
Hepatitis D	
070.42	HEP DELTA W/O MENTION ACTV HEP B DZ W/HEP COMA
070.52	HEP DELTA W/O MENTION ACTV HEP B DZ/HEP COMA
Hepatitis E	
070.43	HEPATITIS E WITH HEPATIC COMA
070.53	HEPATITIS E W/O MENTION HEPATIC COMA
Non-Specific or Other Specified Hepatitis	
070.49	OTHER SPECIFIED VIRAL HEPATITIS W/HEPATIC COMA
070.59	OTH SPEC VIRAL HEP WITHOUT MENTION HEP COMA
070.6	UNSPECIFIED VIRAL HEPATITIS WITH HEPATIC COMA
070.9	UNSPEC VIRAL HEPATITIS WITHOUT MENTION HEP COMA
571.40	UNSPECIFIED CHRONIC HEPATITIS
571.41	CHRONIC PERSISTENT HEPATITIS
571.49	OTHER CHRONIC HEPATITIS
571.8	OTHER CHRONIC NONALCOHOLIC LIVER DISEASE

CODE	DESCRIPTION
571.9	UNSPEC CHRONIC LIVER DISEASE W/O MENTION OF ALCOHOL
573.1	HEPATITIS IN VIRAL DISEASES CLASSIFIED ELSEWHERE
573.2	HEPATITIS OTH INFECTIOUS DISEASES CLASS ELSW
V02.6	VIRAL HEPATITIS CARRIER.
V02.60	VIRAL HEPATITIS CARRIER, UNSPECIFIED
V02.69	OTHER VIRAL HEPATITIS CARRIER
072.71	MUMPS HEPATITIS
078.5	CYTOMEGALIC INCLUSION VIRUS HEPATITIS
091.62	SECONDARY SYPHILITIC HEPATITIS
Autoimmune Hepatitis	
571.42	AUTOIMMUNE HEPATITIS
Hemochromatosis	
275.0	DISORDERS OF IRON METABOLISM
Wilson's Disease	
275.1	DISORDERS OF COPPER METABOLISM
Cancer in the Liver and Biliary Tree	
155.0	CA LIVER, PRIMARY.
155.1	MALIGNANT NEOPLASM OF INTRAHEPATIC BILE DUCTS
155.2	MALIGNANT NEOPLASM LIVER NOT SPEC AS PRIMARY/SEC
197.7	SECONDARY MALIGNANT NEOPLASM OF LIVER
230.8	CARCINOMA IN SITU OF LIVER AND BILIARY SYSTEM
Cancer of the Pancreas	
157.0	MALIGNANT NEOPLASM OF HEAD OF PANCREAS
157.1	MALIGNANT NEOPLASM OF BODY OF PANCREAS
157.2	MALIGNANT NEOPLASM OF TAIL OF PANCREAS
157.3	MALIGNANT NEOPLASM OF PANCREATIC DUCT
157.4	MALIGNANT NEOPLASM OF ISLETS OF LANGERHANS
157.8	MALIGNANT NEOPLASM OF OTHER SPEC SITES OF PANCREAS
157.9	MALIGNANT NEOPLASM OF PANCREAS, PART UNSPECIFIED
Alcoholic Liver Disease	
571.0	ALCOHOLIC FATTY LIVER
571.1	ACUTE ALCOHOLIC HEPATITIS
571.2	ALCOHOLIC CIRRHOSIS OF LIVER
571.3	UNSPECIFIED ALCOHOLIC LIVER DAMAGE
Non-Alcoholic Fatty Liver Disease	
578.1	OTHER CHRONIC NON-ALCOHOLIC LIVER DISEASE
Alpha-1-Antitrypsin Deficiency	

CODE	DESCRIPTION
273.4	ALPHA 1 ANTITRYPSIN DEFICIENCY

Non-Specific Cirrhosis	
571.5	CIRRHOSIS OF LIVER WITHOUT MENTION OF ALCOHOL
Primary Biliary Cirrhosis	
571.6	PRIMARY BILIARY CIRRHOSIS
Hepatic Decompensation	
456.0	ESOPHAGEAL VARICES WITH BLEEDING
456.1	ESOPHAGEAL VARICES WITHOUT MENTION OF BLEEDING
456.20	ESOPHAGEAL VARICES W/BLEED DISEASES CLASS ELSW
456.21	ESOPH VARICES W/O MENTION BLEED DZ CLASS ELSW
567.0	PERITONITIS INFECTIOUS DISEASES CLASSIFIED ELSW
567.2	OTHER SUPPURATIVE PERITONITIS
567.23	PERITONITIS, SPONTANEOUS BACTERIAL
567.8	OTHER SPECIFIED PERITONITIS
567.9	UNSPECIFIED PERITONITIS
572.3	PORTAL HYPERTENSION
789.5	ASCITES
789.59	ASCITES
Liver Abscess	
572.0	ABSCESS OF LIVER
Other Chronic Liver Disease	
573.0	CHRONIC PASSIVE CONGESTION OF LIVER
573.4	HEPATIC INFARCTION
573.9	UNSPECIFIED DISORDER OF LIVER
Biliary Tract Obstructions	
574.00	CALCUS OF GLBLDR W ACUTE CHOLECYSTITIS W/O MENT OBS
574.01	CALCUS OF GLBLDR W ACUTE CHOLECYSTITIS W OBSTRUCTION
574.10	CALCUS OF GLBLDR W OTHER CHOLECYSTITIS W/O MENT OBS
574.11	CALCUS OF GLBLDR W OTHER CHOLECYSTITIS W OBSTRUCTION
574.20	CALCUS OF GLBLDR W/O MENT CHOLECYSTITIS W/O MENT OBS
574.21	CALCUS OF GLBLDR W/O MENT CHOLECYSTITIS W OBSTRUCTION
574.30	CALCUS OF BILE DUCT W ACUTE CHOLECYSTITIS W/O MENT OBS
574.31	CALCUS OF BILE DUCT W ACUTE CHOLECYSTITIS W OBS
574.40	CALCUS OF BILE DUCT W OTHER CHOLECYSTITIS W/O MENT OBS
574.41	CALCUS OF BILE DUCT W OTHER CHOLECYSTITIS W OBS
574.50	CALCUS OF BILE DUCT W/O MENT CHOLECYSTITIS W/O MENT OBS

CODE	DESCRIPTION
574.51	CALCUS OF BILE DUCT W/O MENT CHOLECYSTITIS W OBS
574.60	CALCUS GLBLDR AND BILE DUCT W ACUTE CHOLECYST W/O OBS
574.61	CALCUS GLBLDR AND BILE DUCT W ACUTE CHOLECYST W OBS
574.70	CALCUS GLBLDR AND BILE DUCT W OTH CHOLECYST W/O OBS
574.71	CALCUS GLBLDR AND BILE DUCT W OTH CHOLECYST W OBS
574.80	CALCUS GLBLDR & BILE DUCT W AC & CHR CHOLECYST W/O OBS
574.81	CALCUS GLBLDR & BILE DUCT W AC & CHR CHOLECYST W OBS
574.90	CALCUS GLBLDR AND BILE DUCT W/O CHOLECYST W/O OBS
574.91	CALCUS GLBLDR AND BILE DUCT W/O CHOLECYST W OBS
575.0	ACUTE CHOLECYSTITIS
575.10	CHOLECYSTITIS, UNSPECIFIED
575.11	CHRONIC CHOLECYSTITIS
575.12	ACUTE AND CHRONIC CHOLECYSTITIS
575.2	OBSTRUCTION OF GALLBLADDER
575.3	HYDROPS OF GALLBLADDER
575.4	PERFORATION OF GALLBLADDER
575.5	FISTULA OF GALLBLADDER
575.6	CHOLESTEROLOSIS OF GALLBLADDER
575.8	OTHER SPECIFIED DISORDERS OF GALLBLADDER
575.9	UNSPECIFIED DISORDER OF GALLBLADDER
Cholangitis	
576.1	CHOLANGITIS

D. APPENDIX D. INTERNATIONAL CLASSIFICATION OF DISEASES, NINTH REVISION, CLINICAL MODIFICATION (ICD-9-CM) CODES TO IDENTIFY CHRONIC LIVER DISEASES.

CODE	DESCRIPTION
Hepatitis B	
070.32	VIRAL HEP B W/O HEP COMA CHRN W/O HEP DELTA
070.33	VIRAL HEP B W/O MENTION HEP COMA CHRN W/HEP DELTA
V02.61	HEPATITIS B CARRIER
Hepatitis C	
070.54	CHRONIC HEPATITIS C WITHOUT MENTION HEPATIC COMA
070.70	UNSPECIFIED VIRAL HEPATITIS C W/O HEPATIC COMA
V02.62	HEPATITIS C CARRIER
Non-Specific or Other Specified Hepatitis	
070.59	OTH SPEC VIRAL HEP WITHOUT MENTION HEP COMA
070.9	UNSPEC VIRAL HEPATITIS WITHOUT MENTION HEP COMA
571.40	UNSPECIFIED CHRONIC HEPATITIS
571.41	CHRONIC PERSISTENT HEPATITIS
571.49	OTHER CHRONIC HEPATITIS
V02.6	VIRAL HEPATITIS CARRIER
V02.60	VIRAL HEPATITIS CARRIER, UNSPECIFIED
V02.69	OTHER VIRAL HEPATITIS CARRIER
Autoimmune Hepatitis	
571.42	AUTOIMMUNE HEPATITIS
Hemochromatosis	
275.0	DISORDERS OF IRON METABOLISM
Wilson's Disease	
275.1	DISORDERS OF COPPER METABOLISM
Alcoholic Liver Disease	
571.0	ALCOHOLIC FATTY LIVER
571.1	ACUTE ALCOHOLIC HEPATITIS
571.2	ALCOHOLIC CIRRHOSIS OF LIVER
571.3	UNSPECIFIED ALCOHOLIC LIVER DAMAGE
Alpha-1-Antitrypsin Deficiency	
273.4	ALPHA 1 ANTITRYPSIN DEFICIENCY

E. APPENDIX E. INTERNATIONAL CLASSIFICATION OF DISEASES, NINTH REVISION, CLINICAL MODIFICATION (ICD-9-CM) CODES TO IDENTIFY EXCLUSIONARY CASES OF PRE-EXISTING LIVER/BILIARY DISEASES AMONG CASES WITH CHRONIC LIVER DISEASE.

CODE	DESCRIPTION
Hepatitis B	
070.22	VIRAL HEP B W/HEP COMA CHRN W/O MENTION HEP DELTA
070.23	HEPATITIS B, CHRONIC, W HEPATIC COMA, W HEPATITIS DELTA
Hepatitis C	
070.44	CHRONIC HEPATITIS C WITH HEPATIC COMA
070.71	UNSPECIFIED VIRAL HEPATITIS C WITH HEPATIC COMA
Hepatitis D	
070.42	HEP DELTA W/O MENTION ACTV HEP B DZ W/HEP COMA
070.52	HEP DELTA W/O MENTION ACTV HEP B DZ/HEP COMA
Hepatitis E	
070.43	HEPATITIS E WITH HEPATIC COMA
070.53	HEPATITIS E W/O MENTION HEPATIC COMA
Non-Specific or Other Specified Hepatitis	
070.49	OTHER SPECIFIED VIRAL HEPATITIS W/HEPATIC COMA
070.6	UNSPECIFIED VIRAL HEPATITIS WITH HEPATIC COMA
573.1	HEPATITIS IN VIRAL DISEASES CLASSIFIED ELSEWHERE
573.2	HEPATITIS OTH INFECTIOUS DISEASES CLASS ELSW
072.71	MUMPS HEPATITIS
078.5	CYTOMEGALIC INCLUSION VIRUS HEPATITIS
091.62	SECONDARY SYPHILITIC HEPATITIS
Cancer in the Liver and Biliary Tree	
155.0	CA LIVER, PRIMARY.
155.1	MALIGNANT NEOPLASM OF INTRAHEPATIC BILE DUCTS
155.2	MALIGNANT NEOPLASM LIVER NOT SPEC AS PRIMARY/SEC
197.7	SECONDARY MALIGNANT NEOPLASM OF LIVER
230.8	CARCINOMA IN SITU OF LIVER AND BILIARY SYSTEM
Cancer of the Pancreas	
157.0	MALIGNANT NEOPLASM OF HEAD OF PANCREAS
157.1	MALIGNANT NEOPLASM OF BODY OF PANCREAS
157.2	MALIGNANT NEOPLASM OF TAIL OF PANCREAS
157.3	MALIGNANT NEOPLASM OF PANCREATIC DUCT
157.4	MALIGNANT NEOPLASM OF ISLETS OF LANGERHANS
157.8	MALIGNANT NEOPLASM OF OTHER SPEC SITES OF PANCREAS

CODE	DESCRIPTION
157.9	MALIGNANT NEOPLASM OF PANCREAS, PART UNSPECIFIED
Hepatic Decompensation	
456.0	ESOPHAGEAL VARICES WITH BLEEDING
456.1	ESOPHAGEAL VARICES WITHOUT MENTION OF BLEEDING
456.20	ESOPHAGEAL VARICES W/BLEED DISEASES CLASS ELSW
456.21	ESOPH VARICES W/O MENTION BLEED DZ CLASS ELSW
567.0	PERITONITIS INFECTIOUS DISEASES CLASSIFIED ELSW
567.2	OTHER SUPPURATIVE PERITONITIS
567.23	PERITONITIS, SPONTANEOUS BACTERIAL
567.8	OTHER SPECIFIED PERITONITIS
567.9	UNSPECIFIED PERITONITIS
572.3	PORTAL HYPERTENSION
789.5	ASCITES
789.59	ASCITES
Liver Abscess	
572.0	ABSCESS OF LIVER
Other Chronic Liver Disease	
573.0	CHRONIC PASSIVE CONGESTION OF LIVER
573.4	HEPATIC INFARCTION
573.9	UNSPECIFIED DISORDER OF LIVER
Biliary Tract Obstructions	
574.00	CALCUS OF GLBLDR W ACUTE CHOLECYSTITIS W/O MENT OBS
574.01	CALCUS OF GLBLDR W ACUTE CHOLECYSTITIS W OBSTRUCTION
574.10	CALCUS OF GLBLDR W OTHER CHOLECYSTITIS W/O MENT OBS
574.11	CALCUS OF GLBLDR W OTHER CHOLECYSTITIS W OBSTRUCTION
574.20	CALCUS OF GLBLDR W/O MENT CHOLECYSTITIS W/O MENT OBS
574.21	CALCUS OF GLBLDR W/O MENT CHOLECYSTITIS W OBSTRUCTION
574.30	CALCUS OF BILE DUCT W ACUTE CHOLECYSTITIS W/O MENT OBS
574.31	CALCUS OF BILE DUCT W ACUTE CHOLECYSTITIS W OBS
574.40	CALCUS OF BILE DUCT W OTHER CHOLECYSTITIS W/O MENT OBS
574.41	CALCUS OF BILE DUCT W OTHER CHOLECYSTITIS W OBS
574.50	CALCUS OF BILE DUCT W/O MENT CHOLECYSTITIS W/O MENT OBS
574.51	CALCUS OF BILE DUCT W/O MENT CHOLECYSTITIS W OBS
574.60	CALCUS GLBLDR AND BILE DUCT W ACUTE CHOLECYST W/O OBS
574.61	CALCUS GLBLDR AND BILE DUCT W ACUTE CHOLECYST W OBS
574.70	CALCUS GLBLDR AND BILE DUCT W OTH CHOLECYST W/O OBS
574.71	CALCUS GLBLDR AND BILE DUCT W OTH CHOLECYST W OBS

CODE	DESCRIPTION
574.80	CALCUS GLBLDR & BILE DUCT W AC & CHR CHOLECYST W/O OBS
574.81	CALCUS GLBLDR & BILE DUCT W AC & CHR CHOLECYST W OBS
574.90	CALCUS GLBLDR AND BILE DUCT W/O CHOLECYST W/O OBS
574.91	CALCUS GLBLDR AND BILE DUCT W/O CHOLECYST W OBS
575.0	ACUTE CHOLECYSTITIS
575.10	CHOLECYSTITIS, UNSPECIFIED
575.11	CHRONIC CHOLECYSTITIS
575.12	ACUTE AND CHRONIC CHOLECYSTITIS
575.2	OBSTRUCTION OF GALLBLADDER
575.3	HYDROPS OF GALLBLADDER
575.4	PERFORATION OF GALLBLADDER
575.5	FISTULA OF GALLBLADDER
575.6	CHOLESTEROLOSIS OF GALLBLADDER
575.8	OTHER SPECIFIED DISORDERS OF GALLBLADDER
575.9	UNSPECIFIED DISORDER OF GALLBLADDER
Cholangitis	
576.1	CHOLANGITIS

F. APPENDIX F. DATA PARTNER EXTRACTION FORM AND CHECKLIST

Mini-Sentinel

SEVERE ACUTE LIVER INJURY 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. 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.	Admission Date	No (0)	Yes (1)
3.	Actual Day of Admission (within +/- one day specified date)	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.**		

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IV. International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) Diagnosis Codes

1.	**570** (Acute hepatic necrosis)	No (0)	Yes (1)
2.	**572.2** (Hepatic encephalophathy)	No (0)	Yes (1)
3.	**572.4** (Hepatorenal syndrome)	No (0)	Yes (1)
4.	**572.8** (Liver failure, NOS)	No (0)	Yes (1)
5.	**V42.7** (Liver transplant)	No (0)	Yes (1)
6.	**573.3** (Toxic hepatitis)	No (0)	Yes (1)
7.	**573.8** (Other liver disorders)	No (0)	Yes (1)
8.	Please specify the primary/principal discharge diagnosis code: _____		

V. Attachments: Chart Components

1.	Admission History and Physical (H&P)	No (0)	Yes (1)
2.	Discharge Summary	No (0)	Yes (1)
3.	Transfer Records	No (0)	Yes (1)
4.	Physician Progress Notes (all specialties)	No (0)	Yes (1)
5.	Autopsy Reports / Death Notes	No (0)	Yes (1)
6.	Liver Biopsy Pathology Reports	No (0)	Yes (1)
7.	Laboratory Reports	No (0)	Yes (1)
8.	Inpatient Medication Administration Record	No (0)	Yes (1)
9.	Imaging Reports	No (0)	Yes (1)

VI. Attachments: Additional Data Elements

1.	Liver Biopsy Claims	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.

G. APPENDIX G. INSTRUCTION MANUAL FOR COMPLETING THE DATA PARTNER EXTRACTION FORM

Mini-Sentinel

SEVERE ACUTE LIVER INJURY VALIDATION
Instruction Manual for Completing Data Partner Extraction Form

The purpose of the Data Partner Extraction Form is to collect data from the medical record to use in the validation of discharge diagnosis codes for Severe Acute Liver Injury (SALI). The SALI may be the reason for the hospitalization or it may be that the SALI occurs while the patient is hospitalized for an unrelated diagnosis. There should be only one hospitalization per extraction.

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 hospitalization from the chart in the format MM/DD/YYYY.

3. Extraction Date:
   Date the extraction of the medical record 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. Other (please specify)

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

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III. Patient Identification Verification

Please compare the information on the medical record 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. Admission Date:
   This item relates to the date the patient was admitted to the hospital. If the patient was transferred from another hospital or an emergency room, the date of admission will be that date on which the patient was admitted to the initial hospital. Indicate "yes" if the admission date is the same in the chart as specified in the administrative data. Indicate "no" if the admission date is different in the chart than specified in the administrative data.

3. Actual Day of Admission (+/- one day of specified date):
   Indicate if the date specified in the administrative data is +/- one day of the date of admission in the hospital medical record.

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. International Classification of Diseases, 9th Revision, Clinical Modification (ICD-9-CM) Diagnosis Codes

1-7. For each item, please indicate whether the patient had any of the following diagnosis codes during this hospitalization by circling "Yes" or "No." Use the billing face sheet and the electronic claims data for reference.

8. Please specify the primary or principal discharge diagnosis code (as indicated on the billing face sheet and the electronic claims data) in the space provided.

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V. 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 hospitalization (please refer to Service Dates in Section I), indicating for each a "Yes" or "No" for its inclusion. Please write the case ID number on all attachments in the upper right hand corner.

1. Admission History and Physical (H&P)
2. Discharge Summary
3. Transfer Records
4. Physician Progress Notes* (for all specialties)
5. Autopsy Reports/Death Notes
6. Liver Biopsy Pathology Reports
7. Laboratory Reports*
8. Inpatient Medication Administration Record*
9. Imaging Reports: Head CT and Head/Brain MRI Reports

*Do NOT redact the date that the physician progress notes were written, the date of the laboratory reports, or the date of the medication record.

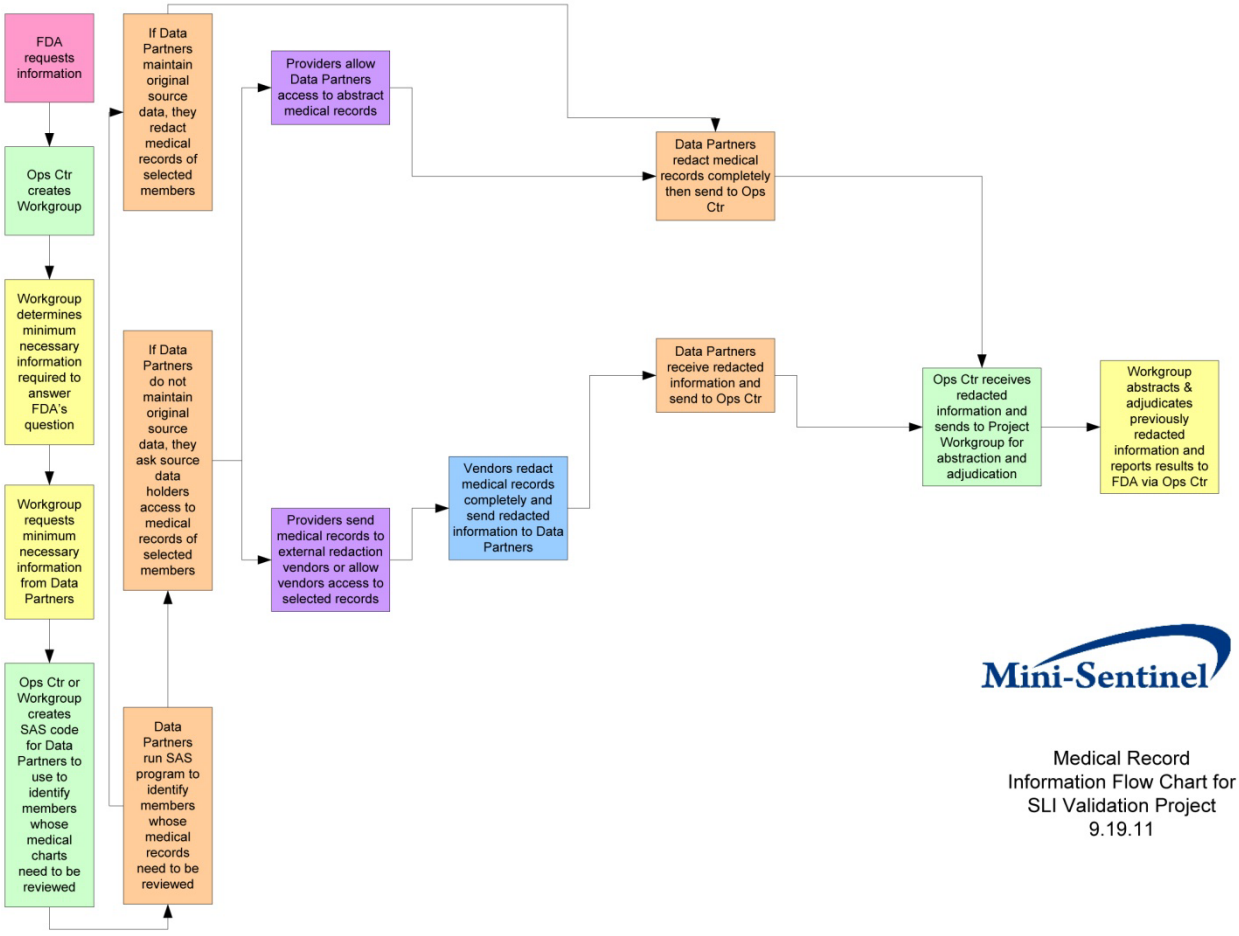
VI. Attachments: Additional Data Elements

Please attach a listing of the following elements for the time period specified below. Indicate if the data elements are attached by circling "Yes" or "No." Please write the case ID number on all attachments in the upper right hand corner.

1. Liver Biopsy Claims
   Indicate "Yes" if a listing of claims for liver biopsies within 182 days before or after the hospital admission date is attached. Liver biopsy claims should be identified by CPT codes (i.e., 47000, 47001, or 47100) and ICD-9 Procedure codes (i.e., 50.11, 50.12, 50.13, 50.14, or 50.91). Indicate "No" if a listing of liver biopsy claims is not attached. Please use electronic claims data to provide this information.

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.

H. APPENDIX H. INFORMATION FLOW CHART FOR THE MINI-SENTINEL SEVERE ACUTE LIVER INJURY (SALI) VALIDATION PROJECT



I. APPENDIX I. LIST OF INTERNATIONAL CLASSIFICATION OF DISEASES, NINTH REVISION, CLINICAL MODIFICATION (ICD-9-CM) AND CURRENT PROCEDURAL TERMINOLOGY (CPT) CODES TO IDENTIFY A LIVER BIOPSY.

CODE TYPE	CODE NUMBER	DESCRIPTION
ICD-9-CM	50.1x	DIAGNOSTIC PROCEDURE ON LIVER
ICD-9-CM	50.9x	OPERATION ON LIVER
CPT	47000	PERCUTANEOUS NEEDLE BIOPSY OF LIVER
CPT	47001	PERCUTANEOUS NEEDLE BIOPSY OF LIVER (AT TIME OF OTHER MAJOR PROCEDURE)
CPT	47100	OPEN BIOPSY OF LIVER

J. APPENDIX J. DATA ABSTRACTION FORM

__ __ __ __ Study ID

__ __ __ MRA Initials

Sample: ____ No Pre-Existing Liver Disease

__ __ / __ __ / __ __ __ __ Admission Date

__ __ / __ __ / __ __ __ __ Discharge Date

____ Chronic Hepatitis B or C

Mini-Sentinel Severe Acute Liver Injury Validation Data Abstraction Form

Instructions: Provide a response for each question. If you are uncertain about a response, or if a condition is written in a physician's note but the diagnosis is not confirmed, circle "Unconfirmed".

Section 1.A. Diagnosis of Severe Acute Liver Injury During Hospitalization

Circle *Yes* or *No*: Please circle if the patient was diagnosed with any of the conditions listed below **in a discharge summary, admission note history and physical examination, progress note by a hepatologist or gastroenterologist, or other physician's note.**

1.	Acute liver (or hepatic) failure (ALF) OR Fulminant liver (or hepatic) failure	No..... 0 Yes..... 1 Unconfirmed..... 8
	If yes, date first diagnosed (mm/dd/yyyy):	__ __ / __ __ / __ __ __ __
2.	"Shock liver"	No..... 0 Yes..... 1 Unconfirmed..... 8
	If yes, date first diagnosed (mm/dd/yyyy):	__ __ / __ __ / __ __ __ __
3.	Hepatic encephalopathy OR Encephalopathy	No..... 0 Yes..... 1 Unconfirmed..... 8
	If yes, date first diagnosed (mm/dd/yyyy):	__ __ / __ __ / __ __ __ __
4.	Drug-induced liver injury OR Drug-induced hepatitis	No..... 0 Yes..... 1 Unconfirmed..... 8
	If yes, date first diagnosed (mm/dd/yyyy):	__ __ / __ __ / __ __ __ __
5.	Acute liver injury OR Acute hepatitis	No..... 0 Yes..... 1 Unconfirmed..... 8
	If yes, date first diagnosed (mm/dd/yyyy):	__ __ / __ __ / __ __ __ __

__ __ __ __ Study ID

__ __ __ MRA Initials

Sample: ____ No Pre-Existing Liver Disease

__ __ / __ __ / __ __ __ __ Admission Date

__ __ / __ __ / __ __ __ __ Discharge Date

____ Chronic Hepatitis B or C

Section 1.B. Causes of Severe Acute Liver Injury

If the answer to every question on the previous page is *No*: Please circle *N/A* for each question in Section 1.B., then proceed to Section 1.C. on page 3.

If the answer to any question on the previous page is *Yes* or *Unconfirmed*: Please circle if the patient was reported to have any of the following causes of severe acute liver injury listed during hospitalization in a physician's note.

		No	Yes	Uncon-firmed	N/A	If yes, date 1st recorded (mm/dd/yyyy)
6.	Acute viral hepatitis ***If no, circle N/A for questions 6a – 6f.***	0	1	8	9	__ __ / __ __ / __ __ __ __
	6a. Hepatitis A	0	1	8	9	__ __ / __ __ / __ __ __ __
	6b. Hepatitis B	0	1	8	9	__ __ / __ __ / __ __ __ __
	6c. Hepatitis C	0	1	8	9	__ __ / __ __ / __ __ __ __
	6d. Hepatitis D	0	1	8	9	__ __ / __ __ / __ __ __ __
	6e. Hepatitis E	0	1	8	9	__ __ / __ __ / __ __ __ __
	6f. Other viral hepatitis causes, (e.g VZV, herpes simplex) _____ _____	0	1	8	9	__ __ / __ __ / __ __ __ __
7.	Autoimmune hepatitis	0	1	8	9	__ __ / __ __ / __ __ __ __
8.	Wilson's disease	0	1	8	9	__ __ / __ __ / __ __ __ __
9.	Acute fatty liver of pregnancy	0	1	8	9	__ __ / __ __ / __ __ __ __

__ __ __ __ Study ID
__ __ __ MRA Initials
Sample: ____ No Pre-Existing Liver Disease

__ __/__ __/__ __ __ __ Admission Date
__ __/__ __/__ __ __ __ Discharge Date
____ Chronic Hepatitis B or C

Section 1.B. Causes of Severe Acute Liver Injury *(continued)*

10.	Drug- or dietary supplement-induced *If no, skip to question #11.*	No..... 0 Yes..... 1 Unconfirmed..... 8 N/A..... 9
	10a. If yes or unconfirmed, specify drug or dietary supplement, if implicated.	_____ _____
	10b. If yes or unconfirmed, was an overdose or suicide attempt implicated?	No..... 0 Yes..... 1 Unconfirmed..... 8 N/A..... 9
11.	Ischemic injury *If no, skip to question #12.* *Terms to look for include "shock liver," "hypotension," "hypotension related to sepsis," "Budd-Chiari," "hepatic vein thrombosis," "hepatic ischemia," "ischemic hepatitis," "hepatic vein thrombosis," "hepatic veno-occlusive disease," "reduced blood flow to liver"*	No..... 0 Yes..... 1 Unconfirmed..... 8 N/A..... 9
	11a. If yes, what is the type of ischemic injury? *Hypotension aka "shock liver"* *Hepatic vein thrombosis aka "Budd-Chiari syndrome"*	Hypotension..... 1 Hepatic vein thrombosis... 2 Unconfirmed..... 8 N/A..... 9
12.	Other causes *Please specify (e.g., sepsis):* _____ _____ _____ _____	No..... 0 Yes..... 1 Unconfirmed..... 8 N/A..... 9

Section 1.C. Liver Biopsy

Circle *Yes* or *No*: Please circle one response below.

13.	Patient received a liver biopsy during hospitalization or within 182 days prior to the hospitalization.	No..... 0 Yes..... 1 Unconfirmed..... 8
	If yes, specify the results of the biopsy: _____ _____	
	Please attach a redacted copy of the biopsy report to this abstraction form.	

__ __ __ __ Study ID

__ __ __ MRA Initials

Sample: ____ No Pre-Existing Liver Disease

__ __ / __ __ / __ __ __ __ Admission Date

__ __ / __ __ / __ __ __ __ Discharge Date

____ Chronic Hepatitis B or C

Section 1.D. Chronic Liver Disease

Circle *Yes* or *No*: Please circle if the patient was reported to have a diagnosis of any of the below conditions in **in a discharge summary, admission note history and physical examination, progress note by a hepatologist or gastroenterologist, or other physician's note.**

		No	Yes	Uncon-firmed	If yes, date 1st recorded (mm/dd/yyyy)
14.	Chronic Hepatitis C	0	1	8	__ __ / __ __ / __ __ __ __
15.	Chronic Hepatitis B	0	1	8	__ __ / __ __ / __ __ __ __
16.	Chronic Hepatitis D	0	1	8	__ __ / __ __ / __ __ __ __
17.	Alcoholic liver disease	0	1	8	__ __ / __ __ / __ __ __ __
18.	Cancer in the liver (primary or metastatic)	0	1	8	__ __ / __ __ / __ __ __ __
19.	Cirrhosis	0	1	8	__ __ / __ __ / __ __ __ __
20.	Autoimmune hepatitis	0	1	8	__ __ / __ __ / __ __ __ __
21.	Wilson's disease	0	1	8	__ __ / __ __ / __ __ __ __
22.	Hemochromatosis	0	1	8	__ __ / __ __ / __ __ __ __
23.	Hepatic decompensation (or end-stage liver disease)	0	1	8	__ __ / __ __ / __ __ __ __
24.	Sclerosing cholangitis	0	1	8	__ __ / __ __ / __ __ __ __
25.	Alpha-1-Antitrypsin deficiency	0	1	8	__ __ / __ __ / __ __ __ __
26.	History of liver transplant	0	1	8	__ __ / __ __ / __ __ __ __
27.	Other chronic liver disease: _____ _____	0	1	8	__ __ / __ __ / __ __ __ __

__ __ __ __ Study ID
__ __ __ MRA Initials
Sample: ____ No Pre-Existing Liver Disease

__ __ / __ __ / __ __ __ __ Admission Date
__ __ / __ __ / __ __ __ __ Discharge Date
____ Chronic Hepatitis B or C

For the following four sections, please circle *Yes* or *No*:
The patient was reported to have any of the following conditions or procedures documented in a discharge summary, admission note, or progress note during hospitalization.

Section 1.E. Jaundice During Hospitalization

28.	Patient had jaundice during hospitalization	No..... 0 Yes..... 1 Unconfirmed..... 8
	If yes, date first recorded (mm/dd/yyyy):	__ __ / __ __ / __ __ __ __

Section 1.F. Mechanical Ventilation During Hospitalization

29.	Mechanical ventilation (also termed “intubated” or “vented”) during hospitalization	No..... 0 Yes..... 1 Unconfirmed..... 8
	If yes, date first recorded (mm/dd/yyyy):	__ __ / __ __ / __ __ __ __

Section 1.G. Receipt of Liver Transplant

30.	Patient underwent work-up for liver transplant during hospitalization	No..... 0 Yes..... 1 Unconfirmed..... 8
	If yes, date first recorded (mm/dd/yyyy):	__ __ / __ __ / __ __ __ __
31.	Patient received a liver transplant during hospitalization	No..... 0 Yes..... 1 Unconfirmed..... 8
	If yes, date first recorded (mm/dd/yyyy):	__ __ / __ __ / __ __ __ __

Section 1.H. Death During Hospitalization

32.	Patient died during hospitalization	No..... 0 Yes..... 1 Unconfirmed..... 8
	If yes, date of death (mm/dd/yyyy):	__ __ / __ __ / __ __ __ __

__ __ __ __ Study ID
__ __ __ MRA Initials
Sample: ____ No Pre-Existing Liver Disease

__ __ / __ __ / __ __ __ __ Admission Date
__ __ / __ __ / __ __ __ __ Discharge Date
____ Chronic Hepatitis B or C

Section 1.I. Diagnosis of Encephalopathy During Hospitalization

If the answer to Question 3 (page 1) is *No*: Please circle *N/A* for each question in Section 1.I., then proceed to Section 1.J. on page 7.

If the patient was reported to have encephalopathy during hospitalization (i.e., if the answer to Question 3 is *Yes* or *Unconfirmed*): Please circle if any of the following conditions were documented during hospitalization in a physician's note.

		No	Yes	Uncon-firmed	N/A	If yes, date 1st recorded (mm/dd/yyyy)
33.	Asterixis (liver flap)	0	1	8	9	__ __ / __ __ / __ __ __ __
34.	Altered mentation or delirium; change, decline in mental status	0	1	8	9	__ __ / __ __ / __ __ __ __
35.	Decreased consciousness	0	1	8	9	__ __ / __ __ / __ __ __ __
36.	Incoherence; dysarthria	0	1	8	9	__ __ / __ __ / __ __ __ __
37.	Confusion; not aware of surroundings; disorientation; amnesia	0	1	8	9	__ __ / __ __ / __ __ __ __
38.	Lethargy; drowsy; somnolent; sleepy	0	1	8	9	__ __ / __ __ / __ __ __ __
39.	Seizure	0	1	8	9	__ __ / __ __ / __ __ __ __
40.	Coma; unresponsive; not arousable	0	1	8	9	__ __ / __ __ / __ __ __ __

__ __ __ __ Study ID
__ __ __ MRA Initials
Sample: ____ No Pre-Existing Liver Disease

__ __/__ __/__ __ __ __ Admission Date
__ __/__ __/__ __ __ __ Discharge Date
____ Chronic Hepatitis B or C

Section 1.J. Data Abstracted from Head CT and/or Head/Brain MRI Imaging Reports

Circle *Yes* or *No*: Please circle if the patient had any of the following imaging procedures during the hospitalization.

41.	Head CT scan	No..... 0 Yes..... 1 Unconfirmed..... 8
	If yes, date of first head CT scan (mm/dd/yyyy):	__ __/__ __/__ __ __ __
42.	Head (or brain) MRI scan	No..... 0 Yes..... 1 Unconfirmed..... 8
	If yes, date of first head or brain MRI scan (mm/dd/yyyy):	__ __/__ __/__ __ __ __

If both of the above are *No*, please circle *N/A* for all remaining questions in this section, then proceed to the next section.

If either of the above is *Yes*, please circle *Yes* or *No*: Were any of the following findings documented in a head CT scan or head/brain MRI report during the hospitalization?

		No	Yes	Uncon-firmed	N/A	If yes, date 1st recorded (mm/dd/yyyyy)
42a.	Cerebral edema	0	1	8	9	__ __/__ __/__ __ __ __
42b.	Uncal herniation	0	1	8	9	__ __/__ __/__ __ __ __
42c.	NEW or acute stroke	0	1	8	9	__ __/__ __/__ __ __ __
42d.	NEW or acute cerebral ischemia	0	1	8	9	__ __/__ __/__ __ __ __
42e.	Intracranial or cerebral bleed or hemorrhage; hemorrhage in a lobe of the brain	0	1	8	9	__ __/__ __/__ __ __ __
42f.	Intracranial or cerebral mass lesion	0	1	8	9	__ __/__ __/__ __ __ __

__ __ __ __ Study ID
__ __ / __ __ / __ __ __ __ Admission Date
__ __ __ MRA Initials
__ __ / __ __ / __ __ __ __ Discharge Date
Sample: ____ No Pre-Existing Liver Disease
____ Chronic Hepatitis B or C

Section 1.K. Medications to Treat Hepatic Encephalopathy During Hospitalization

Circle *Yes* or *No*: Please review the patient's medication lists throughout the hospitalization and circle if the patient was administered any of the following medications during the hospitalization.

		No	Yes	If yes, date of initial administration (mm/dd/yyyy)
43.	Lactulose	0	1	__ __ / __ __ / __ __ __ __
44.	IV mannitol	0	1	__ __ / __ __ / __ __ __ __
45.	IV hypertonic saline	0	1	__ __ / __ __ / __ __ __ __
46.	Methylprednisolone	0	1	__ __ / __ __ / __ __ __ __
47.	Thiopental	0	1	__ __ / __ __ / __ __ __ __
48.	Pentobarbital	0	1	__ __ / __ __ / __ __ __ __
49.	Rifaximin	0	1	__ __ / __ __ / __ __ __ __
50.	Flumazenil	0	1	__ __ / __ __ / __ __ __ __

Section 1.L. Anticoagulation Medication During Hospitalization

Circle *Yes* or *No*: Please review the patient's medication lists throughout the hospitalization and circle if the patient received an anticoagulant during the hospitalization that would affect the prothrombin time.

51.	Coumadin Or Warfarin	No..... 0 Yes..... 1
	If yes, date of initial administration (mm/dd/yyyy):	__ __ / __ __ / __ __ __ __
52.	Argatroban	No..... 0 Yes..... 1
	If yes, date of initial administration (mm/dd/yyyy):	__ __ / __ __ / __ __ __ __

__ __ __ __ Study ID

__ __ __ MRA Initials

Sample: ____ No Pre-Existing Liver Disease

__ __/__ __/__ __ __ __ Admission Date

__ __/__ __/__ __ __ __ Discharge Date

____ Chronic Hepatitis B or C

Section 1.M. Laboratory Results During Hospitalization

Please review the patient's laboratory results during the hospitalization and record the units, reference range, value, and date of the first and highest results for each of the following .

	Lab	Units	Reference Range	1st Result	Date of 1st result (mm/dd/yyyy)	Highest Result	Date of highest result (mm/dd/yyyy)
53.	ALT	____	_____	_____	__/__/____	_____	__/__/____
54.	AST	____	_____	_____	__/__/____	_____	__/__/____
55.	INR	____	_____	_____	__/__/____	_____	__/__/____
56.	Total Bilirubin	____	_____	_____	__/__/____	_____	__/__/____
57.	Indirect Bilirubin	____	_____	_____	__/__/____	_____	__/__/____
58.	Direct Bilirubin	____	_____	_____	__/__/____	_____	__/__/____
59.	Alk Phos	____	_____	_____	__/__/____	_____	__/__/____
60.	GGT	____	_____	_____	__/__/____	_____	__/__/____
61.	Ammonia	____	_____	_____	__/__/____	_____	__/__/____
62.	Ethanol	____	_____	_____	__/__/____	_____	__/__/____
63.	Aceta-minophen	____	_____	_____	__/__/____	_____	__/__/____
64.	Other drug: _____	____	_____	_____	__/__/____	_____	__/__/____

__ __ __ __ Study ID

__ __ __ MRA Initials

Sample: ____ No Pre-Existing Liver Disease

__ __/__ __/__ __ __ __ Admission Date

__ __/__ __/__ __ __ __ Discharge Date

____ Chronic Hepatitis B or C

Section 1.M. Laboratory Results During Hospitalization *(cont'd)*

Please review the patient's laboratory results during the hospitalization and record the units, reference range, value, and date of the initial result for each of the following serologies.

	Lab	Units	Reference Range	Initial Result	Date of Initial Result (mm/dd/yyyy)
65.	Hep A IgG	_____	_____	_____	__/__/____
66.	Hep A IgM	_____	_____	_____	__/__/____
67.	HBsAg	_____	_____	_____	__/__/____
68.	Hep B Core IgM	_____	_____	_____	__/__/____
69.	HCV Antibody	_____	_____	_____	__/__/____
70.	Hep C RNA	_____	_____	_____	__/__/____
71.	HDV Antibody	_____	_____	_____	__/__/____
72.	HEV Antibody	_____	_____	_____	__/__/____
73.	CMV IgG	_____	_____	_____	__/__/____
74.	AFP	_____	_____	_____	__/__/____
75.	ANA	_____	_____	_____	__/__/____
76.	ASMA	_____	_____	_____	__/__/____
77.	AMA	_____	_____	_____	__/__/____
78.	LKM-1	_____	_____	_____	__/__/____
79.	Cerulo-plasmin	_____	_____	_____	__/__/____

__ __ __ __ Study ID
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Sample: ____ No Pre-Existing Liver Disease

__ __/__ __/__ __ __ __ Admission Date
__ __/__ __/__ __ __ __ Discharge Date
____ Chronic Hepatitis B or C

Section 1.N. Transfer Status

Circle *Yes* or *No*: Please circle one response below.

80.	Patient was transferred from an outside hospital	No..... 0 Yes..... 1 Unconfirmed..... 8
Please attach a redacted copy of the transfer report to this abstraction form.		

Section 1.O. Discharge Summary

Please attach to this data abstraction form a copy of the discharge summary for this hospitalization, redacted of personal identifiers.

Section 1.P. Abstractor's Comments

Please use the space below to provide additional information that will help the arbitrators to adjudicate the clinical event.

81.	Abstractor's Comments: _____

Section 1.Q. Racial Information

Circle *Yes* or *No*: Please circle one response below to indicate the patient's race.

82.	Patient race	White..... 1 Non-white..... 2 Unconfirmed..... 8

Thank you! Abstraction is complete.

If there is uncertainty regarding any answers for this patient, please check with a physician before forwarding this form to the endpoints adjudicators.

K. APPENDIX K. ADJUDICATION FORM

__ __ __ __ Study ID

__ __ __ MRA Initials

Sample: ____ No Pre-Existing Liver Disease

__ __ / __ __ / __ __ __ __ Admission Date

__ __ / __ __ / __ __ __ __ Discharge Date

____ Chronic Hepatitis B or C

Section 2. Adjudicator's Assessment of Severe Acute Liver Injury

Section 2 should be completed by the adjudicators only.

To the adjudicator: Please identify yourself and classify the event by circling one response for each item below.

83.	Name of Adjudicator	Kimberly Forde. . ..... 1 David Goldberg..... 2 Raj Reddy..... . 3
84.	Classification of severe acute liver injury event	Definite severe acute liver injury… 1 No severe acute liver injury……... 2 Unable to determine…….. 3
85.	Classification of acute liver failure	Definite acute liver failure…….. 1 No acute liver failure ……..... 2 Unable to determine…….. 3 Not applicable (patient identified with toxic hepatitis)…….. 4

To the adjudicator: Please use the space below to provide comments, if necessary.

86.	Adjudicator's Comments: _____

Appendix L. Timeline for the completion of the Mini-Sentinel severe acute liver injury (SALI) validation

Task	Description of Task	Target Date	Actual Date
Task 1	Identify workgroup members and create workgroup	6/6/11	**6/6/11**
Task 2	Develop electronic coding algorithm for identifying possible severe acute liver injury cases	6/6/11 – 8/24/11	**6/6/11 – 8/24/11**
Task 3	Finalize definition of severe acute liver injury	6/6/11 – 9/7/11	**6/6/11 – 9/7/11**
Task 4	Develop, test, revise and finalize abstraction and adjudication form	9/7/11 – 12/7/11	**9/7/11 – 10/7/11**
Task 5	**5a**. Establish contacts/process at each Data Partner for chart request **5b**. Develop sampling strategy to identify and retrieve charts of possible severe acute liver injury cases **5c**. Develop, test, and finalize SAS program to distribute to Data Partners to identify and sample potential severe acute liver injury cases	9/15/11 – 12/14/11	**11/16/11– 1/25/12**
Task 6	**6a**. Request, obtain, and redact charts of cases **6b**. Forward all electronic copies of redacted charts to Operations Center **6c**. Send Penn charts for abstraction and adjudication	12/14/11 – 2/28/12	**TYPE 1& 2: 12/16/11 – 6/30/12** **TYPE 3: 12/16/11 – 6/30/12**
	Provide ongoing feedback to FDA on validation of severe acute liver injury codes (during workgroup calls)	4/15/12 – 5/1/12	**12/16/11 – 8/6/12**
Task 7	Perform data abstraction for cases without pre-existing liver/biliary diseases (Type 1 & 2)	1/1/12 – 3/14/12	**2/8/12 – 7/6/12**
Task 8	Perform data abstraction for cases with chronic liver disease (Type 3)	1/1/12 – 3/14/12	**3/28/12 – 7/6/12**
Task 9	Perform case adjudication for cases without pre-existing liver/biliary diseases (Type 1 & 2)	2/1/12 – 4/1/12	**4/1/12 – 7/13/12**
Task 10	Perform case adjudication for cases with chronic liver disease (Type 3)	2/1/12 – 4/1/12	**6/4/12 – 7/13/12**
Task 11	Conduct data analysis on validation of severe acute liver injury codes (all types)		**6/4/12 – 8/6/12**
Task 12	Compose draft report for review by Protocol Core, Operations Center and FDA	5/15/12 – 6/15/12	**7/23/12 – 8/7/12**
Task 13	MSOC and FDA provide feedback to Mini-Sentinel Severe Acute Liver Injury workgroup	6/15/12 – 6/29/12	**8/7/12 – 8/21/12**
Task 14	Revise and submit final report on adjudication results (including record accession and completeness rates for requested records), and presentation of findings to FDA	7/15/12	**8/21/12 – 9/12/12**
Task 15	Submit manuscript for publication/present at FDA webinar	7/31/12	**TBD**