SENTINEL ASSESSMENT PROTOCOL

TRANSFUSION RELATED ACUTE LUNG INJURY AFTER RED BLOOD CELL, PLASMA AND PLATELET ADMINISTRATION 2013-2015

Prepared by: Candace C. Fuller, MPH, PhD,[1] Lesley H. Curtis, PhD,[2] Steven A. Anderson, PhD, MPP,[3] Carolyn Balsbaugh, MPH,[1] Nicholas Bryant, BBA,[4] Howard Chazin, MD, MBA,[3] Pamela Clark, MD, JD,[3] Richard Forshee, PhD,[3] Jason Hickok, MBA, RN[4] Stacey Honda, MD,[5] Richard Max Kaufman, MD,[6] Mikhail Menis, PharmD, MS,[3] Karla M. Miller, PharmD, BCPP,[4] Manette Niu, MD,[3] Wendy Paul, MD,[3] Robert Rosofsky, MA,[7] Azadeh Shoaibi, PhD, MHS,[3] Caren Spencer-Smith, MIS,[4] Jamie L. Todd, MD,[8] Fang Zhang, PhD,[1] Lauren Zichittella, MS,[1] Craig Zinderman, MD, MPH, [3] Meghan A. Baker, MD, ScD[1]

Author Affiliations: 1 Department of Population Medicine, Harvard Medical School and Harvard Pilgrim Health Care Institute, Boston, MA; 2 Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, Duke University Medical Center, Durham, NC; 3 Center for Biologics Evaluation and Research, Food and Drug Administration, Silver Spring, MD; 4 Hospital Corporation of America, Nashville, TN; 5 Kaiser Permanente, Hawaii; 6 Brigham and Women's Hospital Adult Transfusion Service, Harvard Medical School Boston, MA; 7 Health Information Systems Consulting, Milton, MA; 8 Division of Pulmonary, Allergy and Critical Care Medicine, Department of Medicine, Duke University Medical Center, Durham, NC

September 16, 2016

The Sentinel System is sponsored by the U.S. Food and Drug Administration (FDA) to proactively monitor the safety of FDA-regulated medical products and complements other existing FDA safety surveillance capabilities. The Sentinel System is one piece of FDA's Sentinel Initiative, a long-term, multi-faceted effort to develop a national electronic system. The Blood Safety Continuous Active Surveillance Network (BloodSCAN) is the Sentinel component for the safety surveillance of blood products and blood components. Sentinel Collaborators include Data and Academic Partners that provide access to healthcare data and ongoing scientific, technical, methodological, and organizational expertise. The Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223201400030I. This project was funded by the FDA through HHS Mini-Sentinel contract number HHSF223200910006I.

Sentinel Assessment Protocol

Protocol-based Assessment of Transfusion Related Acute Lung Injury after Red Blood Cell, Plasma and Platelet Administration

Table of Contents

I. INTRODUCTION

The Blood Safety Continuous Active Surveillance Network (BloodSCAN), is a component of the Sentinel System initiated by the Center for Biologics Evaluation and Research (CBER) as an active surveillance system that focuses on evaluating recipient safety of FDA-regulated blood components and plasma-derived products. The BloodSCAN framework utilizes billing and other electronic health data within the Sentinel System to assess the risk of adverse health outcomes of interest following exposure to blood products among large populations. The ability to assess population risk of blood-product related adverse events complements spontaneous reporting of adverse events to FDA and other existing FDA safety surveillance programs.

In 2016, FDA expanded the data within Sentinel to include inpatient electronic health data from Hospital Corporation of America (HCA). This assessment, which is the first Sentinel utilization of this new inpatient data source, examines the feasibility of utilizing HCA's Sentinel database to capture exposure to blood components and the outcome of transfusion-related acute lung injury (TRALI). The assessment will also describe incidence rates of TRALI subsequent to blood component exposure.

II. OBJECTIVES

A. PRIMARY OBJECTIVES

1. To describe identification of potential TRALI cases, risk factors for TRALI, and relevant transfusion exposures in HCA's Sentinel database
2. To describe incidence rates of TRALI subsequent to plasma, platelet, packed red blood cell administration using HCA's Sentinel database
3. To determine through medical chart review the performance of an ICD-9-CM code based algorithm for identifying TRALI
4. To determine through medical chart review the positive predictive value of reported transfused product exposure in identified TRALI cases

B. EXPLORATORY OBJECTIVES

1. To explore the potential for comparing blood component specific TRALI incidence rates
2. To explore the ability to identify specific categories of blood components, including component type and processing method (e.g., leukocyte-reduced, irradiated)
3. To explore methods for reducing any relevant missing transfusion information in HCA's Sentinel database
4. To describe the distribution of possible patient risk factors, such as age, sex, and relevant comorbidities, among cases of TRALI
5. To describe the distribution of possible transfusion risk factors, such as volume of transfusion and component processing (e.g., leukoreduction, irradiation) among cases of TRALI
6. To identify which HCA data elements are included in the Sentinel Common Data Model (SCDM) that are useful/relevant for studying TRALI, and to identify additional inpatient data elements that may be useful but are not included in the SCDM

III. BACKGROUND

A. PUBLIC HEALTH SIGNIFICANCE AND STUDY MOTIVATION

Although blood transfusions are administered in many hospitals on a daily basis, patient and exposure associated risk factors for many non-infectious adverse events are often poorly understood. Transfusion-related Acute Lung Injury (TRALI) is a rare but serious life threatening adverse event which occurs during or within 6 hours of transfusion. TRALI is characterized by respiratory distress and pulmonary edema, and is a leading cause of reported transfusion-related mortality in the United States. Despite voluntary measures taken by the transfusion community to reduce risk of TRALI, 41% of transfusion-related fatalities reported to the U.S. Food and Drug Administration between years 2010 and 2014 were attributed to TRALI.[1] TRALI is difficult to diagnose, relies on clinician case recognition skills, and commonly accepted case definitions have varied over time, likely resulting in under- or inconsistent recognition. Reporting of TRALI is not universally required in the United States, although blood transfusion services are required to report fatal complications of blood transfusions to the FDA. These challenges leave us with an incomplete understanding of the epidemiology and attributable burden of these serious transfusion-related pulmonary complications. Risk factors in recipients (e.g., smoking status)[2] and in transfused blood products (e.g., antibodies, bioreactive substances, older RBC storage age)[3] have been noted, and only recently have been described in general populations of transfused patients. Availability of large administrative and electronic healthcare databases is providing new opportunities to examine serious but rare transfusion associated adverse events such as TRALI.[2,4-6]

Ultimately, development of a surveillance system to monitor adverse events following transfusion of blood and blood products/components could inform FDA regulatory actions and impact physicians' ability to assess and potentially mitigate risks for individual patients.

B. HOSPITAL CORPORATION OF AMERICA

Hospital Corporation of America (HCA) is a leading provider of inpatient services, operating in 20 states and the United Kingdom. HCA is comprised of locally managed facilities, and currently includes more than 165 hospitals and 115 freestanding surgery centers. Nearly 5 percent of all inpatient care delivered in the United States is provided by HCA facilities; this currently includes approximately 26 million patient encounters per year.[7] As a large network of acute inpatient hospitals as well as other facilities, HCA provides a unique new set of data to the Sentinel distributed data network.

HCA became a full Sentinel Data Partner in January 2016, and has transformed available data into the Sentinel Common Data Model (SCDM).[8] Status as a full Sentinel data partner signifies that the Sentinel Operations Center (SOC) has approved the HCA's Sentinel database as SCDM-compliant, quality-checked and query-able. The HCA Sentinel database currently includes approximately 2 million inpatient encounters per year, as well as emergency room and outpatient visits to HCA facilities. HCA's data transformation includes two new Sentinel tables (current structure of these tables is included in Appendix A), which capture inpatient pharmacy and inpatient transfusion data.

C. INPATIENT RED BLOOD CELL, PLASMA AND PLATELET ADMINISTRATION

More than 90% of blood transfusions in the United States are performed in inpatient settings.[9] The 2013 National Blood Collection and Utilization Survey includes estimates for the amount of blood collected and transfused in the United States per year.[10] This report estimates 13,180,000 whole blood (WB) and red blood cell (RBC) units were transfused in the United States in 2013. Estimates of platelets transfused totaled 2,281,000 units (including 128,000 whole blood derived platelets and 2,137,000 apheresis

platelets). An estimated 3,624,000 units of plasma were also transfused. Thus, in 2013 the most commonly transfused blood component pertaining to this protocol was RBCs, followed by plasma, and platelets. These numbers provide some context in terms of what may be expected in terms of blood components transfused per year in HCA hospitals.

D. TRANSFUSION-RELATED ACUTE LUNG INJURY (TRALI)

TRALI is a leading cause of transfusion related fatalities in the United States.[1] Broadly, TRALI is defined as the onset of respiratory distress during or within 6 hours of blood transfusion.[11] TRALI is relatively rare, and the estimated U.S. incidence of TRALI has varied widely across studies.[12-14] This variation may be partially attributed to the lack of population-based TRALI studies and focus on specific hospitals or centers, but studies in critically ill patients have noted higher TRALI incidence rates.[12] However, a recent population-based study examining TRALI occurrence in elderly Medicare beneficiaries estimated an overall rate of 22.5 per 100,000 transfused inpatient stays.[4] TRALI has been associated with transfusions of RBCs, fresh frozen plasma (FFP), and platelets.[15,16] It has also been reported rarely after intravenous immunoglobulin treatment.[17, 18]

TRALI is a syndrome for which no specific clinical test is available and diagnosis is based on clinical, laboratory and radiological parameters.[6,11] The Centers for Disease Control and Prevention National Healthcare Safety Network [19] has defined TRALI as new onset of acute lung injury (ALI) occurring during or within 6 hours of blood transfusion (**Table 1**). The term 'Possible TRALI' is used when there is a temporal relationship to an alternative ALI risk factor (**Table 2**). Additionally, the literature suggests that some patients may meet the TRALI definition, but have symptoms beginning outside of the six hour post-transfusion window, and thus a delayed TRALI definition has been suggested to capture such patients.[12,20]

Table 1: Transfusion Related Acute Lung Injury (TRALI) definitions

Definition	Clinical Description
Definitive TRALI[19]	1. No evidence of acute lung injury (ALI) prior to transfusion AND 2. ALI onset during or within 6 hours of transfusion AND 3. Hypoxemia defined by any of these methods: •PaO2 / FiO2 ≤300 mm Hg •Oxygen saturation is < 90% on room air •Other clinical evidence AND 4. Radiographic evidence of bilateral infiltrates AND 5. No evidence of left atrial hypertension (i.e. circulatory overload) AND 6. No temporal relationship to an alternative risk factor for ALI during or within 6 hours of completion of transfusion
Possible TRALI[19]	Same as above EXCEPT there is a temporal relationship to a specific ALI risk factor (Table 2)
Delayed TRALI definition, defined in critically ill patients	
Delayed TRALI[12,20]	Same as for possible TRALI except allows for symptom onset within 6 to 72 hours of blood transfusion

Table 2: Alternate risk factors for Acute Lung Injury (ALI)[19]

Direct Lung Injury	Indirect lung injury
Aspiration	Severe sepsis
Pneumonia	Shock
Toxic inhalation	Multiple trauma
Lung contusion	Burn injury
Near drowning	Acute pancreatitis
	Cardiopulmonary bypass
	Drug overdose

TRALI is believed to be caused by immune mediated mechanisms that lead to neutrophil activation, damage to endothelial cells, and pulmonary edema.[21] A two-hit hypothesis[11,22] has been suggested for TRALI, with the first hit associated with patient risk factors that result in primed neutrophils adhering to the patient's pulmonary endothelium. The second hit may be antibody-mediated or non-antibody mediated, but relates to blood transfusion mediators activating endothelial cells and pulmonary neutrophils causing capillary leakage and thus pulmonary edema.

According to the two hit model, risk factors for TRALI are both patient and transfusion dependent.[21] Blood products containing plasma have been commonly associated with TRALI, and HLA antibodies in blood products containing plasma from female donors specifically have been implicated.[23] Blood product age (i.e., longer storage) may play a role.[24] Numerous patient risk factors have been implicated, and include sepsis, cardiac surgery, trauma, and other ALI risk factors.[11] Higher incidence of TRALI has also been reported in patients with alcohol use disorder, patients who smoke cigarettes, and in patients with end stage liver disease.[12,20] ICU patients have also been reported to have a higher incidence of TRALI, presumably due to underlying co-morbidities.[20,25]

IV. METHODS

A. STUDY POPULATION AND DATA SOURCES

This assessment will include HCA hospitals systematically contributing inpatient transfusion data to the Sentinel Distributed Database (SDD). The population will consist of all hospitalized individuals with evidence of a transfusion during the period of interest, September2013 through September 2015. This time period was selected because prior to September 2013 many HCA hospitals were not systematically providing transfusion data.

Within this period, individuals will be included in the analyses if they had evidence of TRALI (defined below) in HCA's Sentinel database or b) had evidence of a transfusion of a relevant blood component/product (defined below) in HCA data. This project will also attempt to confirm TRALI and transfusion information for TRALI cases through medical chart review. As HCA is a new Sentinel Data Partner, exploratory analyses will focus on feasibility of examining patient and transfusion risk factors in HCA data, as well as identification of blood components, including component type and processing method (e.g., leukocyte-reduced, irradiated). We will use information derived from medical chart review to inform these explorations.

B. STUDY DESIGN AND OVERVIEW OF ANALYSIS PLAN

A retrospective cohort study design is proposed to examine TRALI occurrence among HCA patients transfused in a hospital inpatient setting between September 2013 and September 2015. Within this cohort, capture of potential TRALI cases, risk factors for TRALI, and relevant transfusion exposures in HCA's Sentinel database will be described, and incidence rates of TRALI subsequent to plasma, platelet, packed red blood cell administration using HCA's Sentinel database will be calculated. Medical chart reviews will be conducted to confirm the outcome (TRALI) and the transfusion exposure, and the positive predictive values of each electronic algorithm will be evaluated. The gold standard will be medical chart confirmed outcomes and transfusion exposures.

Unadjusted TRALI rates (per 100,000 inpatient transfusion stays) will be calculated overall, by year, blood component groups, sex, age, race, and number of units transfused. If appropriate transfused unit data are available, unadjusted TRALI rates per number of units transfused will also be calculated. Medical charts will be utilized to confirm the TRALI outcome and transfusion exposure in identified TRALI cases, and the positive predictive value of an ICD-9-CM based algorithm for identifying TRALI will be presented. Similarly, the positive predictive value of reported transfused product exposure and medical chart confirmed exposure in identified TRALI cases will be presented.

As HCA is a new Sentinel Data Partner, exploratory analyses are included as feasibility analyses (see page 2). The workgroup will explore the potential to compare blood component specific TRALI rates, examine TRALI patient and transfusion risk factors, and ability to identify specific categories of blood components, including component type and processing method (e.g., leukocyte-reduced, irradiated). Finally, the workgroup will describe which HCA data elements are included in the SCDM that are useful/relevant for studying TRALI, and which inpatient data elements could be useful but have not been included, and to assess the feasibility and need for adding these elements based on their availability, accuracy, and usefulness for blood and other biological products.

The plan is shown schematically below:

Relative Timing	Method	Analysis	Data to use
Initial	Descriptive analysis examining capture of potential TRALI cases, risk factors for TRALI, and relevant transfusion exposures	Primary	Transfusions: HCA Sentinel Data Outcome: HCA Sentinel Data
	Descriptive analyses, examining potential to compare blood component specific TRALI unadjusted rates	Exploratory	Transfusions: HCA Sentinel Data Outcome: HCA Sentinel Data
	Descriptive analyses, examining: • ability to identify specific categories of blood components, including component type and processing method (e.g., leukocyte-reduced, irradiated) • methods for reducing any relevant missing transfusion information in HCA's Sentinel database • distribution of possible patient risk	Exploratory	Transfusions: HCA Sentinel Data Outcome: HCA Sentinel Data

Relative Timing	Method	Analysis	Data to use
	factors, such as age, sex, and relevant comorbidities, among cases of TRALI • distribution of possible transfusion risk factors, such as volume of transfusion, indication, pregnancy history, component processing (e.g., leukoreduction, irradiation) among cases of TRALI • transfusion stays with TRALI vs without TRALI, comparing demographic characteristics (age, gender, race), length of stay, mechanical ventilation (identified with ICD-9-CM procedure codes) and inpatient mortality		
Final	Descriptive analysis, calculating unadjusted rates of TRALI in identified cohort	Primary	Transfusions: HCA Sentinel Data Outcome: HCA Sentinel Data
	Validation of TRALI outcome, in identified TRALI cases	Primary	Transfusions: HCA Sentinel Data Outcome: HCA Sentinel Data and Chart Review
	Validation of transfusion exposure in identified TRALI cases	Primary	Transfusions: HCA Sentinel Data Outcome: HCA Sentinel Data and Chart Review
	Descriptive analysis identifying which HCA data elements are included in the SCDM that are useful/relevant for studying TRALI, and which inpatient data elements could be useful but have not been included, and to assess the feasibility and need for adding these elements based on their availability, accuracy, and usefulness for blood and other biological products	Exploratory	Transfusions: HCA Sentinel Data Outcome: HCA Sentinel Data

C. EXPOSURES OF INTEREST

Primary objectives of this protocol require the electronic identification of blood component type (i.e., plasma, platelets, and packed red blood cells) in HCA's Sentinel database. HCA currently utilizes two coding systems to identify transfusions, ISBT 128 and Codabar. These code systems allow for identification of blood component type, and may in theory also allow for identification of processing method (e.g., leukocyte-reduced, irradiated) at HCA. ISBT and Codabar, include > 4,500 codes and > 1,500 codes, respectively. At HCA, historically there has been use of both code types to identify transfusions. Although both systems are still in use at HCA, there has been an increased uptake in use of ISBT codes and a decrease in use of Codabar codes over time. For example, by mid-2015 less than 1% of HCA transfusions were coded with a Codabar code.

Databases of ISBT codes are updated monthly by the International Council for Commonality in Blood Banking Automation, Inc. (ICCBBA), but Codabar codes are no longer updated. Endorsed by the AABB (Advancing Transfusion and Cellular Therapies Worldwide), ICCBBA is an international non-governmental organization (NGO) in official relations with the World Health Organization (WHO) that manages, develops, and licenses ISBT 128, the international information standard for the terminology, coding and labeling of medical products of human origin.[26]

The National Healthcare Safety Network's (NHSN) variable of Prod_CDC[27] will be used in combination with ISBT and Codabar code systems to collapse these lengthy code lists into relevant blood component categories. Categories included in the NHSN system are listed in **Table 3**. Essentially, each ISBT or Codabar code will receive a NHSN label to allow for collapsing of granular codes into relevant categories. The latest version of the NHSN's data dictionary and the ICCBBA's databases available at the time of program development will be used to accomplish this task.

Exploratory objectives included in this protocol require the electronic identification of component processing (e.g., leukoreduction, irradiation) within HCA's Sentinel database. Although highly specific codes exist with the ISBT and Codabar systems which could in theory be used to identify component processing, a thorough exploration of HCA data must occur. There may be missing ISBT or Codabar codes, or codes which are not known to be valid. Thus, there will be an attempt to characterize any relevant missing transfusion information. This characterization may require working with HCA staff to interpret the product information included in the Sentinel Inpatient Transfusion Table (**Table 7**), or other available information. It is possible that local coding across HCA's network may dictate how relevant blood products/components are coded in HCA data, and thus the usefulness of specific codes for identification of blood component processing is unknown. To accomplish exploratory objectives, the same coding systems described above will be used, and the workgroup will work closely with HCA to learn more about coding practices and opportunities to identify component processing within HCA data broadly.

Additional exposure related variables to be explored in this protocol include transfusion risk factors for TRALI, such as ability to identify transfusion timing, transfusion environment (i.e., ICU, Floor, Operating room), number of transfusions per hospitalization and volume transfused. The feasibility of identifying these variables in the HCA Sentinel database will be explored, and if possible, frequency distribution among TRALI cases will be characterized.

Table 3: Method for categorizing blood products/components the National Healthcare Safety Network (NHSN): Variable Prod_CDC[27]

Broad Categorization	Description
Plasma	APHPLASMA - Apheresis plasma
	WBDPLASMA - Whole blood derived plasma
Platelets	APHPLAT - Apheresis platelets
	IRAPHPLAT - Irradiated apheresis platelets
	IRRAPHPLAT - Irradiated leukocyte reduced apheresis platelets
	IRLRWBDPLAT - Irradiated leukocyte reduced whole blood derived platelets
	IRWBDPLAT - Irradiated whole blood derived platelets
	LRSPHPLAT - Leukocyte reduced apheresis platelets
	LRWBDPLAT - Leukocyte reduced whole blood derived platelets

Broad Categorization	Description
	WBDPLAT - Whole blood derived platelets
Red Blood Cells	APHRBC - Apheresis red blood cells
	IRAPHRBC - Irradiated apheresis red blood cells
	IRLRAPHRBC - Irradiated leukocyte reduced apheresis red blood cells
	IRLRWBDRBC - Irradiated leukocyte reduced whole blood derived RBC
	IRWBDRBC - Irradiated whole blood derived red blood cells
	LRAPHRBC - Leukocyte reduced apheresis red blood cells
	LRWBDRBC - Leukocyte reduced whole blood derived red blood cells
	WBDRBC - Whole blood derived red blood cells
Whole Blood	WB - Whole blood
Other	CRYO – Cryoprecipitate
	GRAN – Granulocytes
	LEUK – Leukocytes
	LYMPH – Lymphocytes
	MNC - Mononuclear cells
	SERUM – Serum

D. OUTCOME DEFINITION

Potential cases of TRALI will be identified with the codes included in **Table 4**. As TRALI is likely under-diagnosed, this protocol focuses not only on the TRALI specific ICD-9-CM code (ICD-9 518.7), but also on specific respiratory failure codes described above in combination with an ICD-9-CM code for a transfusion reaction. **Table 5** includes the electronic criteria to identify potential cases of TRALI in the HCA Sentinel database. These criteria include ICD-9-CM codes, as the time-period of interest for this protocol precedes the transition to ICD-10-CM coding in the United States.

Table 4: Working list of codes for TRALI and transfused ALI

ICD-9-CM Code	Definition
518.7	Transfusion-related acute lung injury
518.81	Acute respiratory failure
518.82	Other pulmonary insufficiency, not elsewhere classified code in any position
999.80	Other infusion and transfusion reaction
999.89	Other transfusion reaction
E934.7	Natural blood and blood products causing adverse effects in therapeutic use

Table 5: Electronic criteria to identify potential cases of TRALI

Criteria	ICD-9-CM Code(s)
Criterion A	TRALI, ICD-9-CM code in any position (518.7)
Criterion B	Acute respiratory failure ICD-9-CM code in any position (518.81), WITH code for a blood transfusion reaction (999.80 or 999.89 or E934.7)
Criterion C	Other pulmonary insufficiency (518.82), WITH code for a blood transfusion reaction (999.80 or 999.89 or E934.7)
Any TRALI Criteria	Criteria A, and/or B, and/or C listed above

The above criteria and codes will be used to identity TRALI cases in HCA's Sentinel database and will be used to calculate incident rates of TRALI subsequent to plasma, platelet and packed red blood cell administration based on the electronic criteria. Stratifications will be made by TRALI criterion as feasible. These TRALI criteria will also be used to identify TRALI cases in HCA's Sentinel database for chart review.

Medical charts will be obtained for relevant cases, reviewed and adjudicated by clinical experts.

This chart information will identify chart validated cases, which will be the gold standard for the primary validation objective. Please see section E.

E. TRALI AND TRANSFUSION EXPOSURE VALIDATION

Medical records of all cases of inpatient diagnosis of TRALI will be reviewed, regardless of transfusion status or timing relative to transfusion. The maximum total number of cases to be reviewed is 200. If the available number of cases exceeds 200, we will use a pre-specified sampling scheme based on the diagnosis criteria to ensure that the highest-priority cases are reviewed.

Charts will be selected based on the following criteria:

1. All charts meeting Criterion A, identified in the time period of interest, will be reviewed
2. Charts meeting Criterion B or C, identified during the time period of interest, will be randomly selected for review, until a total of 200 charts is reached

The workgroup will collaborate with content experts to develop the chart abstraction/adjudication form to ensure all necessary information is collected from the medical records.

In order to identify the cases and obtain the medical charts, we will send programs for HCA to run on their uniform-format patient-level files. These programs will produce a report of the number and characteristics (e.g., age and sex) of the cases. The reports will include information on clinical setting, actual diagnosis, and date of the diagnosis. The list will be returned to HCA who will then attach patient name, HCA medical record number, and provider name and address to all visits. Another program to be run at HCA will organize the list of charts to pull by facility.

The chart of the entire hospitalization will be made available to clinicians who will abstract and adjudicate each case to verify the transfusion exposure and the TRALI diagnosis. Two clinicians will independently review 10 charts, blinded to the other reviewer's decision. This initial round of case classification will enable refinement of the classification rules. Using the refined set of rules, the clinicians will complete a second round of case classification for another 10 cases. If discrepancies between reviewers are eliminated after the second round, then a single reviewer will be utilized for the

remainder of the cases. If discrepancies persist, additional rounds of double review may occur and could continue for the remainder of the case review.

Hospital care setting at the time of TRALI diagnosis (e.g., inpatient, institutional, outpatient, or emergency department), admission type (e.g., emergency, urgent, elective), hospital unit (e.g., coronary care unit, intensive care unit, trauma unit) will also be confirmed and recorded. Transfusion information in identified patients with TRALI will be reviewed to correctly identify the transfusion exposure. For patients with a prior transfusion identified in the HCA Sentinel database, the transfusion record prior to and closest to the TRALI event will be sought, to confirm or correct transfusion date and timing, number of transfused units for each blood component (e.g., RBCs, platelets, plasma, whole blood, autologous transfusion), volume of transfusion, type of blood component transfused, blood component processing (e.g., leukocyte reduced, irradiated) in the HCA Sentinel database. Hospital care setting for the time of transfusion exposure will also be confirmed. The indication for transfusion will be recorded for each patient if present. Use of mechanical ventilation before and after TRALI will also be confirmed. For patients without a prior transfusion recorded in the HCA Sentinel database, if the case is ultimately classified as TRALI, then HCA hospital records will be reviewed to attempt to confirm or correct the absence of a transfusion exposure prior to TRALI onset.

Clinicians will utilize the National Healthcare Safety Network (NHSN) Manual: Biovigilance Component definition of TRALI (summarized in **Table 1** and **Table 2** of this protocol) to diagnose TRALI.[19] Delayed TRALI will be diagnosed in the same manner, but will allow for symptom onset between 6 and 72 hours of the transfusion. The primary analysis will be based on definitive TRALI, secondary analyses will include possible TRALI and delayed TRALI.

Positive predictive value will be determined for each electronic TRALI criterion as compared to definitive TRALI confirmed by clinical adjudicators. PPVs will also be calculated for each electronic TRALI criteria as compared to possible and delayed TRALI as confirmed by clinical adjudicators. The PPV will also be determined for the transfusion exposure as identified in HCA Sentinel data, as compared to confirmed transfusion exposure obtained by clinical adjudicators during chart review.

F. STATISTICAL ANALYSIS

1. Descriptive Analyses

A number of univariate and bivariate descriptive analyses in the form of tables, histograms, and other graphs will be carried out prior to calculating rates of TRALI in order to characterize the transfusion and TRALI data in HCA's Sentinel database. These will include frequency distributions of TRALI cases meeting each TRALI electronic criterion, and frequency distributions of relevant transfusion variables including any relevant missing information. Codabar and ISBT Coding systems utilized by HCA to identify plasma, platelets and packed red blood cells will be explored. The number of potential TRALI inpatient transfusion stays will be identified, and frequencies of specific blood component exposure among inpatient transfusions stays will be presented. If feasible, patient (e.g., smoking status, alcohol abuse, direct lung injury, indirect lung injury, diabetes, COPD, chemotherapy or malignancy) and transfusion (e.g., number of units, blood component transfused) level risk factors of interest will be examined.

Descriptive analyses will also be used to examine TRALI case demographics and patient and transfusion risk factors of interest.

2. Calculation of Incidence Rates

Unadjusted incidence rates of TRALI occurrence after any transfusion will be calculated, along with 95% confidence intervals. Any transfusion will be defined as exposure to plasma, platelets (PLT), or packed red blood cells (RBC) as defined in HCA's Sentinel database. TRALI will be defined using ICD-9-CM based codes in HCA's Sentinel database, and the primary analysis will focus on TRALI as defined by criterion A (**Table 5**). Unadjusted TRALI rates (per 100,000 inpatient transfusion stays) will be stratified by year, blood component groups (i.e., plasma, PLT, and RBC), age, sex, race, and quantified units. If data on the number and type of component unit(s) transfused are available, unadjusted TRALI rates per number of units transfused will also be calculated. If feasible, quantified units will be examined separately for children and adults.

In addition to identifying rates of TRALI occurrence after any exposure to plasma, PLT, or RBC during an inpatient stay, if adequate sample size is available we will also explore exposure to RBC-only, plasma-only, and PLT-only. Exposure to multiple blood component types (i.e., plasma and PLT, RBC and PLT, plasma and RBC, plasma and RBC and PLT) or non-specific blood components (if relevant) will also be described.

3. Quantification of Algorithm Positive Predictive Value

a. Outcome

We will examine the positive predictive value of electronic TRALI criteria and diagnosis codes through chart review. Medical chart review will be conducted to validate transfusion exposure details for all TRALI cases determined to be definitive, possible, or delayed TRALI cases without regard to whether a prior transfusion record existed in the electronic claims data.

Charts will be adjudicated according to the workgroup approved TRALI clinical case definitions. We will quantify the positive predictive value for each electronic TRALI criterion, as compared to chart review. We will consider stratifying results by age and gender, and also including analysis for possible TRALI and delayed TRALI. Information about indications for blood transfusion, history of prior events will also be collected for analysis in exploratory objectives.

b. Exposure

We will examine the positive predictive value of reported transfused blood component exposure (s) of interest as compared to confirmed blood component exposure (s) of interest in identified TRALI cases included in HCA's Sentinel database. Medical chart review will be conducted to validate transfusion exposure details for all TRALI cases determined to be definitive, possible, or delayed TRALI cases without regard to whether a prior transfusion record existed in the electronic data. Medical charts will be reviewed to confirm the blood component exposure, dates and times of exposure, and obtain information about the details of exposure (e.g., if available, the number of units, infusion rate, specific product, processing method, route of administration, transfusion environment). We will quantify the positive predictive value for electronically identified blood component, as compared to blood component exposure confirmed with chart review.

Blood exposures will be identified electronically in HCA's Sentinel database, using the ISBT and Codabar systems and the National Healthcare Safety Network (NHSN)'s blood component mapping system will be used to identify broad blood component categories. Although this primary objective is focused broadly on blood components, if feasible and available, we collect any additional information about blood

component(s) administered (e.g., method of processing) included in charts for analysis in exploratory objectives.

We will use all available data to identify transfusion timing, and will explore the possibility of supplementing chart information with electronically derived timing information (i.e., administration timing as defined in the HCA Sentinel database). In other words, neither the electronic (claims) data nor the medical record data will be pre-specified to be consistently prioritized over the other, rather both will be evaluated and used in establishing the transfusion timing.

4. Exploratory Analyses

The potential for comparing blood component specific TRALI incidence rates will be explored, and if feasible a reference category will be defined for variables examined in the primary analysis and unadjusted rate ratios and 95% confidence intervals will be calculated.

The workgroup will also explore the ability to identify specific categories of blood components within HCA data, including component type and processing method (e.g., leukocyte-reduced, irradiated), and will provide descriptive analyses. If feasible and available, exposure information retrieved from charts, such as method of blood component processing and timing of administration, will be compared to information in HCA's Sentinel transfusion table. Similarly, the feasibility of examining distribution of possible patient level and transfusion level TRALI risk factors not explored in primary analyses and relevant comorbidities will be examined as part of these exploratory analyses.

Descriptive statistical analyses comparing transfusion stays with TRALI vs without TRALI by demographic characteristics (age, gender, race), length of stay, mechanical ventilation (identified with ICD-9-CM procedure codes) and by inpatient mortality will also be conducted.

The workgroup will explore methods to reduce missing transfusion information in HCA's Sentinel database. If feasible, this exploration will utilize internal investigations with HCA staff to determine what may be possible, and/or development of alternate code lists to identify specific transfusion exposures. Finally, the workgroup will identify HCA data elements that are included in the SCDM that are useful/relevant for studying TRALI and data elements relevant to TRALI that are not included in the SCDM.

5. Statistical Power

TRALI is a relatively rare outcome, and the workgroup has estimated that few cases (i.e., <200) may be identified during the time period of interest. Thus, all primary and exploratory analyses to be conducted will likely be descriptive.

V. DATASET CREATION

The distributed Sentinel Common Data Model (SCDM) as populated by HCA will be used for this protocol. This distributed data framework ensures that Sentinel Data Partners maintain control over patient level data. Sentinel Data Partners extract, and organize data from their systems into multiple files of standard formats, of which relevant ones for this study include demographics, encounter, diagnosis, procedure, inpatient transfusion and inpatient pharmacy. Sentinel programmers will provide HCA with programs to run on the standard-format patient-level files, which will produce datasets for analysis. These will be provided to Sentinel analysts using Sentinel's secure file transport methods.

VI. INSTITUTIONAL REVIEW BOARD APPROVAL AND OTHER AUTHORIZATIONS

Per the privacy section on the Mini-Sentinel policies and procedures manual:[1]

> *4.1 Mini-Sentinel Activities Are Public Health Practice, Not Research*
>
> *The HHS Office of Human Research Protections (OHRP) determined that the regulations administered by OHRP (45 CFR Part 46, "Common Rule") do not apply to the activities that are included in the FDA's Sentinel Initiative. FDA stated that this assessment also applies to Mini-Sentinel, as it is part of the Sentinel Initiative.*
>
> *Additionally, FDA determined that Mini-Sentinel activities are public health activities in support of FDA's public health mission. It is therefore not necessary for the Collaborating Institutions to obtain approval from their respective Institutional Review Boards (IRBs) or Privacy Boards, or to obtain waivers of authorization under HIPAA, to participate in Mini-Sentinel activities (45 CFR §164.512(b)).*

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

[1] The Mini-Sentinel policies and procedures manual is currently being updated for Sentinel. The same policies and procedures described above apply because Sentinel, like Mini-Sentinel, is one of the activities included in the FDA's Sentinel Initiative.

VII. REFERENCES

1. Fatalities Reported to FDA Following Blood Collection and Transfusion: Annual Summary for Fiscal Year 2014. (Accessed 03/4/2016, at http://www.fda.gov/downloads/BiologicsBloodVaccines/SafetyAvailability/ReportaProblem/TransfusionDonationFatalities/UCM459461.pdf.)
2. Sridhar G, Menis M, Selvam N, et al. Transfusion-Related Acute Lung Injury (TRALI) Occurrence, Risk Factors, and Outcome: A Nested Case-Control Study. The Internet Journal of Hematology 2013;9.
3. Toy P, Gajic O, Bacchetti P, et al. Transfusion-related acute lung injury: incidence and risk factors. Blood 2012;119:1757-67.
4. Menis M, Anderson SA, Forshee RA, et al. Transfusion-related acute lung injury and potential risk factors among the inpatient US elderly as recorded in Medicare claims data, during 2007 through 2011. Transfusion 2014;54:2182-93.
5. Menis M, Izurieta HS, Anderson SA, et al. Outpatient transfusions and occurrence of serious noninfectious transfusion-related complications among US elderly, 2007-2008: utility of large administrative databases in blood safety research. Transfusion 2012;52:1968-76.
6. Clifford L, Singh A, Wilson GA, et al. Electronic health record surveillance algorithms facilitate the detection of transfusion-related pulmonary complications. Transfusion 2013;53:1205-16.
7. HCA at a Glance | HCA Healthcare. 2016. (Accessed 9/06/2016, at http://hcahealthcare.com/about/hca-at-a-glance.dot.)
8. Sentinel Common Data Model v5.0.1. 2016. (Accessed 04/22/2016, at http://mini-sentinel.org/data_activities/distributed_db_and_data/details.aspx?ID=105.)
9. Reimbursement for blood products and related services. (Accessed August 8, 2013., at http://www.redcrossblood.org/sites/arc/files/arc_seminar_presentation_without_case_studies_-_web_version_4_2012.pdf.)
10. Chung KW, Basavaraju SV, Mu Y, et al. Declining blood collection and utilization in the United States. Transfusion 2016.
11. Vlaar AP, Juffermans NP. Transfusion-related acute lung injury: a clinical review. Lancet 2013.
12. Gajic O, Rana R, Winters JL, et al. Transfusion-related acute lung injury in the critically ill: prospective nested case-control study. Am J Respir Crit Care Med 2007;176:886-91.
13. Popovsky MA, Moore SB. Diagnostic and pathogenetic considerations in transfusion-related acute lung injury. Transfusion 1985;25:573-7.
14. Rana R, Fernandez-Perez ER, Khan SA, et al. Transfusion-related acute lung injury and pulmonary edema in critically ill patients: a retrospective study. Transfusion 2006;46:1478-83.
15. Marik PE, Corwin HL. Efficacy of red blood cell transfusion in the critically ill: a systematic review of the literature. Crit Care Med 2008;36:2667-74.
16. Khan H, Belsher J, Yilmaz M, et al. Fresh-frozen plasma and platelet transfusions are associated with development of acute lung injury in critically ill medical patients. Chest 2007;131:1308-14.
17. Rizk A, Gorson KC, Kenney L, Weinstein R. Transfusion-related acute lung injury after the infusion of IVIG. Transfusion 2001;41:264-8.
18. Eder AF, Herron R, Strupp A, et al. Transfusion-related acute lung injury surveillance (2003-2005) and the potential impact of the selective use of plasma from male donors in the American Red Cross. Transfusion 2007;47:599-607.
19. U.S. Centers for Disease Control and Prevention. The National Healthcare Safety Network (NHSN) Manual: Biovigilance Component v2. In: Division of Healthcare Quality Promotion National Center for Emerging and Zoonotic Infectious Diseases, ed. Atlanta, GA 2016.

20. Benson AB, Moss M, Silliman CC. Transfusion-related acute lung injury (TRALI): a clinical review with emphasis on the critically ill. Br J Haematol 2009;147:431-43.
21. Silliman CC, McLaughlin NJ. Transfusion-related acute lung injury. Blood Rev 2006;20:139-59.
22. Marik PE, Corwin HL. Acute lung injury following blood transfusion: expanding the definition. Crit Care Med 2008;36:3080-4.
23. Sachs UJ, Link E, Hofmann C, Wasel W, Bein G. Screening of multiparous women to avoid transfusion-related acute lung injury: a single centre experience. Transfus Med 2008;18:348-54.
24. Silliman CC, Bjornsen AJ, Wyman TH, et al. Plasma and lipids from stored platelets cause acute lung injury in an animal model. Transfusion 2003;43:633-40.
25. Juffermans NP. Transfusion-related acute lung injury: emerging importance of host factors and implications for management. Expert Rev Hematol 2010;3:459-67.
26. International Council for Commonality in Blood Banking Automation, Inc. 2016. (Accessed 4/15/2016, at https://www.iccbba.org/.)
27. NHSN Data Dictonary -Patient Safety Component January 2015. Centers for Disease Control and Prevention, Division of Healthcare Quality Promotion, National Center for Emerging and Zoonotic Infectious Diseases. , 2015. (Accessed 03/28./2016, at http://www.cdc.gov/nhsn/acute-care-hospital/bio-hemo/.)

VIII. APPENDIX A

Table 6: Inpatient Pharmacy, HCA Table structure as of May 2016

Variable Name	Variable Type and Length (Bytes)*	Values	Definition / Comments / Guideline
PatID	Character(Site specific length)	Unique member identifier	Arbitrary person-level identifier. Used to link across tables. Derivative of HCA Patient Account Number.
EncounterID	Character(Site specific length)	Unique encounter identifier	A unique combination of PatID, ADate, Provider and EncType. Used to link the Encounter, Diagnosis, Procedure, Inpatient Pharmacy, and Inpatient Transfusion tables.
NDC	Character(11)	National Drug Code	Please expunge any place holders (e.g., '-' or extra digit)
RxID	Character(15)	Unique Rx administration identifier	For mapping back to source data
RxADate	Numeric(4)	SAS date value	Rx Administration date
RxATime	Numeric(4)	SAS time value HH:MM	Rx Administration time
RxRoute	Character(10)	Values as developed by HCA	Actual/administered
RxDose	Numeric(8)	Values as developed by HCA	Actual/administered. Format captures maximum # of whole and decimal digits allowed by software technology for numeric data.
RxUOM	Character(10)	Values as developed by HCA	Actual/administered--HCA to develop a standard list of values.

*Technical note: These are attributes of SAS© variables. For numeric values, the number of storage bytes and the number of decimal digits in a value are not identical.

Table 7: Inpatient Transfusion, HCA Table structure as of May 2016

Variable Name	Variable Type and Length (Bytes)*	Values	Definition / Comments / Guideline
PatID	Character(Site specific length)	Unique member identifier	Arbitrary person-level identifier. Used to link across tables. Derivative of HCA Patient Account Number.
EncounterID	Character(Site specific length)	Unique encounter identifier	A unique combination of PatID, ADate, Provider and EncType. Used to link the Encounter, Diagnosis, Procedure, Inpatient Pharmacy, and Inpatient Transfusion tables.
TransID	Character(15)	Unique transfusion administration identifier	For mapping back to source data
TransCode	Character(15)	Code value for an infusion product	Must be paired with the correct TransCode_Type
TransCode_Type	Character(2)	Code type for the value in TransCode	Transfusion product code type. This variable combined with the TransCode variable should be used to capture any type of Inpatient Infusion product in the source data. Other code types will be added as new terminologies are used. IS=ISBT CD=CODABAR
Orig_TransProd	Character(Site specific length)	Original product name/mnemonic	Name of product within Data Partner
BloodType	Character(3)	Blood type: A, B, O, AB (upper case) with RH factor (+, -, or null only)	Blood type and Rh factors, left-justified. Convert any text Rh factor to symbols (e.g., “pos” to “+”, “negative” to “-“). Rh factor can be blank.
TDate_Start	Numeric(4)	SAS date value	Administration start date
TTime_Start	Numeric(4)	SAS time value HH:MM	Administration start time
TDate_End	Numeric(4)	SAS date value	Administration end date
TTime_End	Numeric(4)	SAS time value HH:MM	Administration end time
EncType	Character(2)	ED = Emergency Department	ED encounters only
		IP = Inpatient Hospital Stay	Includes all inpatient stays, same-day hospital discharges, hospital transfers, and acute hospital care where the discharge is after the admission date. This also includes ED visits that become inpatient stays.
		IS = Non-Acute Institutional Stay	Includes hospice, skilled nursing facility (SNF), rehab center, nursing home, residential, overnight non-hospital dialysis and other non-hospital stays.
		OA = Other Ambulatory Visit	Includes other non overnight AV encounters such as hospice visits, home health visits, skilled nursing facility visits, other non-hospital visits, as well as telemedicine, telephone and email consultations.

*Technical note: These are attributes of SAS© variables. For numeric values, the number of storage bytes and the number of decimal digits in a value are not identical.