Validation of transfusion administrations among potential Transfusion-Related Acute Lung Injury (TRALI) patients included in the Sentinel Distributed Database

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- This presentation reflects the views of the authors and not necessarily those of the FDA

Background

- Sentinel Initiative is the U.S. Food and Drug Administration's (FDA) active safety surveillance system that uses routine querying tools and pre-existing electronic healthcare data to monitor safety of medical products
- FDA's Center for Biologics Evaluation and Research (CBER) is responsible for ensuring safety of blood products and blood components
- Blood Safety Surveillance Continuous Active Network (BloodSCAN)
  - Subcomponent of the Sentinel Initiative sponsored by CBER to monitor recipient safety of FDA-regulated blood components and blood-derived products

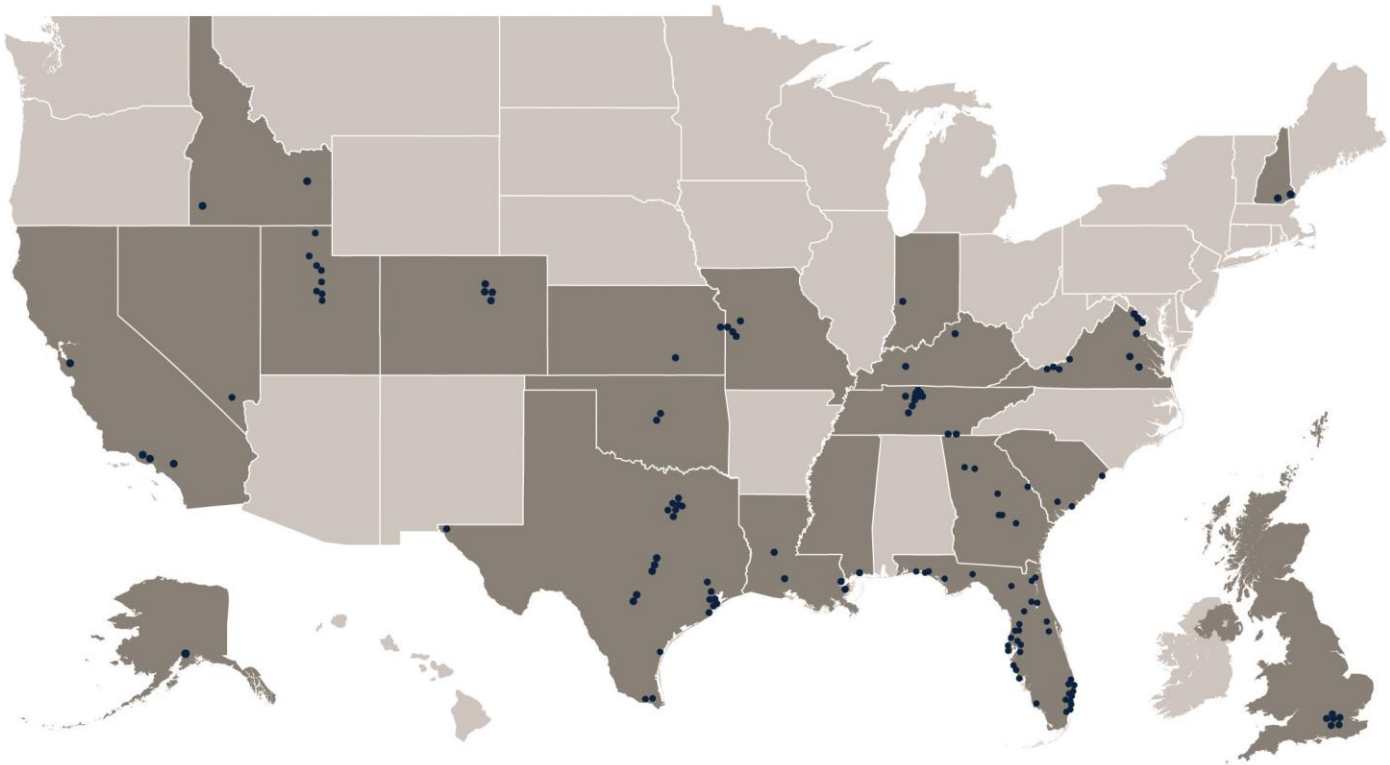
Background

- Many blood transfusions occur in inpatient settings
  - Claims data often do not contain transfusion information

- In 2016, inpatient electronic transfusion data were added to the Sentinel network, providing new safety surveillance potential
  - Full-text electronic health records available
  - Facilitates chart review and exposure/outcome validation during inpatient stays

Background

Sentinel Inpatient EMR Data



174 hospitals located in 20 states

~5% of all inpatient care delivered in USA

Sentinel Common Data Model: Overview

Administrative

Enrollment	Demographic	Dispensing	Encounter	Diagnosis	Procedure
Person ID	Person ID	Person ID	Person ID	Person ID	Person ID
Enrollment start & end dates	Birth date	Dispensing date	Service date(s)	Service dates	Service date(s)
Drug coverage	Sex	National drug code (NDC)	Encounter ID	Encounter ID	Encounter ID
Medical coverage	Zip code	Days supply	Encounter type and provider	Encounter type and provider	Encounter type & provider
Medical record availability	Etc.	Amount dispended	Facility	Diagnosis code & type	Procedure code & type
			Etc.	Principal discharge diagnosis	Etc.

Clinical

Lab Result	Vital Signs
Person ID	Person ID
Result and specimen collection dates	Measurement date & time
Test type, immediacy & location	Height & weight
Logical Observation Identifiers Names and Codes (LOINC®)	Diastolic & systolic BP
Test result & unit	Tobacco use & type
Etc.	Etc.

Registry

Death	Cause of Death	State Vaccine
Person ID	Person ID	Person ID
Death date	Cause of death	Vaccination date
Source	Source	Admission type
Confidence	Confidence	Vaccine code & type
Etc.	Etc.	Provider
		Etc.

Inpatient

Inpatient Pharmacy	Inpatient Transfusion
Person ID	Person ID
Administration date & time	Administration start & end date & time
Encounter ID	Encounter ID
National Drug Code (NDC)	Transfusion administration ID
Route	Transfusion product code
Dose	Blood type
Etc.	Etc.

https://www.sentinelinitiative.org/sentinel/data/distributed-database-common-data-model/sentinel-common-data-model

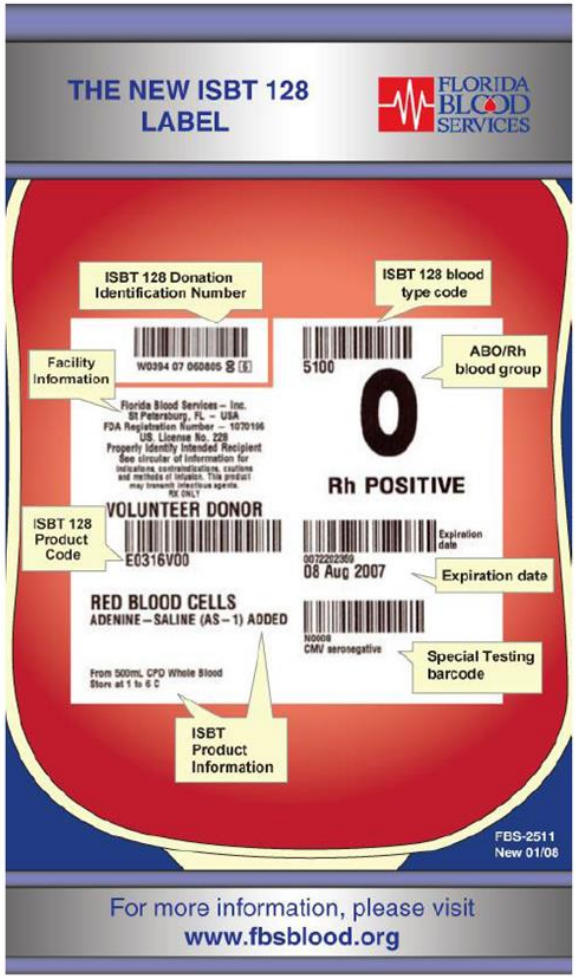
Background: Electronic transfusion data

- Sentinel inpatient electronic transfusion data provides information often not available in claims data:
  - Administered transfusions
  - Start/end transfusion dates AND times
  - Product blood type (A, B, O, AB)
  - Rh factor (+, -)
  - # units, potentially large volume transfusion

Background: Electronic transfusion data

- Two transfusion coding systems in use
  - ISBT-128 codes1 (majority >99%)
  - Codabar codes (<1%)

- ISBT-128 and Codabar codes identify:
  - Blood components
  - Processing/Collection methods



[1]International Council for Commonality in Blood Banking Automation (ICCBBA) https://www.iccbba.org/

Background: Electronic transfusion data

- Centers for Disease Control and Prevention's (CDC) National Healthcare Safety Network's (NHSN) method was used for mapping codes into relevant categories:
  - Blood component (red blood cells [RBC], platelets, plasma, cryoprecipitate)
  - Processing methods (leukocyte-reduction [LR], irradiation [IR])
  - Collection methods (apheresis [AP] or whole blood derived [WBD])

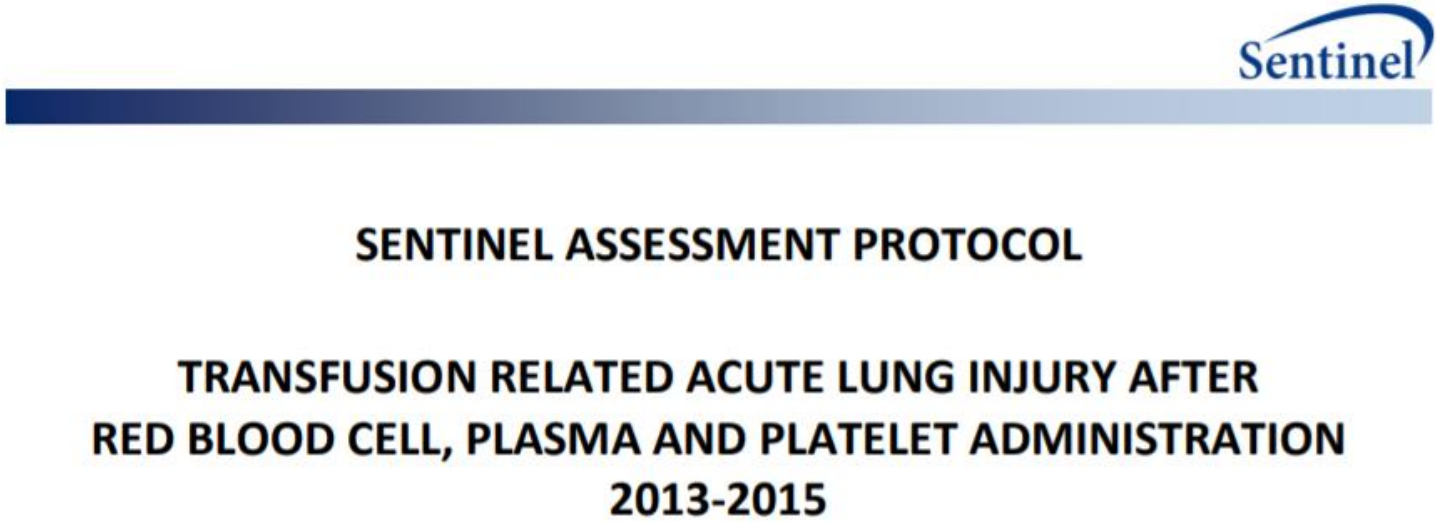
CDC's NHSN Mapping

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
	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

https://www.cdc.gov/nhsn/index.html

Background

- This sub-study was part of a protocol based assessment:



- Assessment identified potential TRALI cases with diagnosis codes in Sentinel data, and validated outcomes and transfusion exposures captured in the Sentinel electronic database with medical charts

https://www.sentinelinitiative.org/sites/default/files/vaccines-blood-biologics/assessments/Sentinel_TRALI-and-Red-Blood-Cell-Plasma-and-Platelet-Administration_Protocol.pdf

Objectives

- To determine through medical chart review the positive predictive value of reported blood transfusion exposures in potential TRALI cases captured in the Sentinel electronic database, specifying:
  - Blood component (RBC, platelets, plasma, cryoprecipitate)
  - Processing methods (LR, IR)
  - Collection methods (AP or WBD)

Methods

Potential TRALI cases with transfusion information in Sentinel electronic data were identified between September 2013-September 2015

Medical chart review: Physicians with critical care expertise confirmed transfusions potentially associated with TRALI

PPV analyses: Transfusion data in Sentinel database compared with transfusion information **confirmed** by the adjudicators (chart **confirmed** transfusions used as gold standard for validation)

Methods

- Potential TRALI inpatient stays identified with diagnosis codes:

TRALI Criterion A

- TRALI ICD-9-CM code (518.7)

TRALI Criterion B

- Acute respiratory failure ICD-9-CM code (518.81), AND code for a blood transfusion reaction (999.80 or 999.89 or E934.7)

TRALI Criterion C

- Other pulmonary insufficiency (518.82), AND code for a blood transfusion reaction (999.80 or 999.89 or E934.7)

Methods

- Sentinel inpatient electronic transfusion data are labeled with ISBT-128 and Codabar codes
- Mapped codes to blood components using CDC's National Healthcare Safety Network's method
- Classified the codes into relevant categories:
  - Blood component (RBC, platelets, plasma, cryoprecipitate)
  - Processing methods (LR, IR)
  - Collection methods (AP or WB)

Methods: Chart review

- Requested medical charts for all potential TRALI cases through the electronic medical records (EMR) platform
  - Requested all charts with a potential TRALI diagnosis code, even if there was no transfusion documented in electronic data
  - Adjudicators were provided with the medical chart of the entire hospitalization for each potential TRALI case
  - Adjudicators abstracted and adjudicated every potential TRALI case and verified the transfusion exposure
  - Blood bank feeds were often not available on the standard EMR platform, but if they were available they were provided to adjudicators for review

Methods: Chart review

- Physicians with critical care expertise confirmed transfusions potentially associated with TRALI, including:
  - blood component, processing, and collection methods

- When transfusion information was not available in charts, physicians described reasons for the omission
  - i.e., transfusion occurred in another hospital, outpatient setting, etc.

Methods: Positive Predictive Value (PPV) calculation

	Transfusions confirmed by adjudicator, Yes	Transfusions confirmed by adjudicator, No
Transfusions in Sentinel electronic data, Yes	A	C
Transfusions in Sentinel electronic data, No	B	D

- We quantified the PPV for transfusions identified in the Sentinel electronic database, as compared to transfusion exposures confirmed with chart review (gold standard)
  - Positive predictive value was calculated as the proportion of transfusions in Sentinel electronic data that was confirmed by medical chart review
    - PPV= A/A+C

Methods

- We examined the PPV of electronic Sentinel transfusion data as compared to medical chart review, and focused on:
  - Any transfusion
  - Blood component (i.e., RBC, plasma, platelet, cryoprecipitate)
  - Processing method (LR, IR)
  - Collection method (i.e., AP or WBD)
- For all analyses, chart confirmed transfusion exposures was the gold standard

Methods

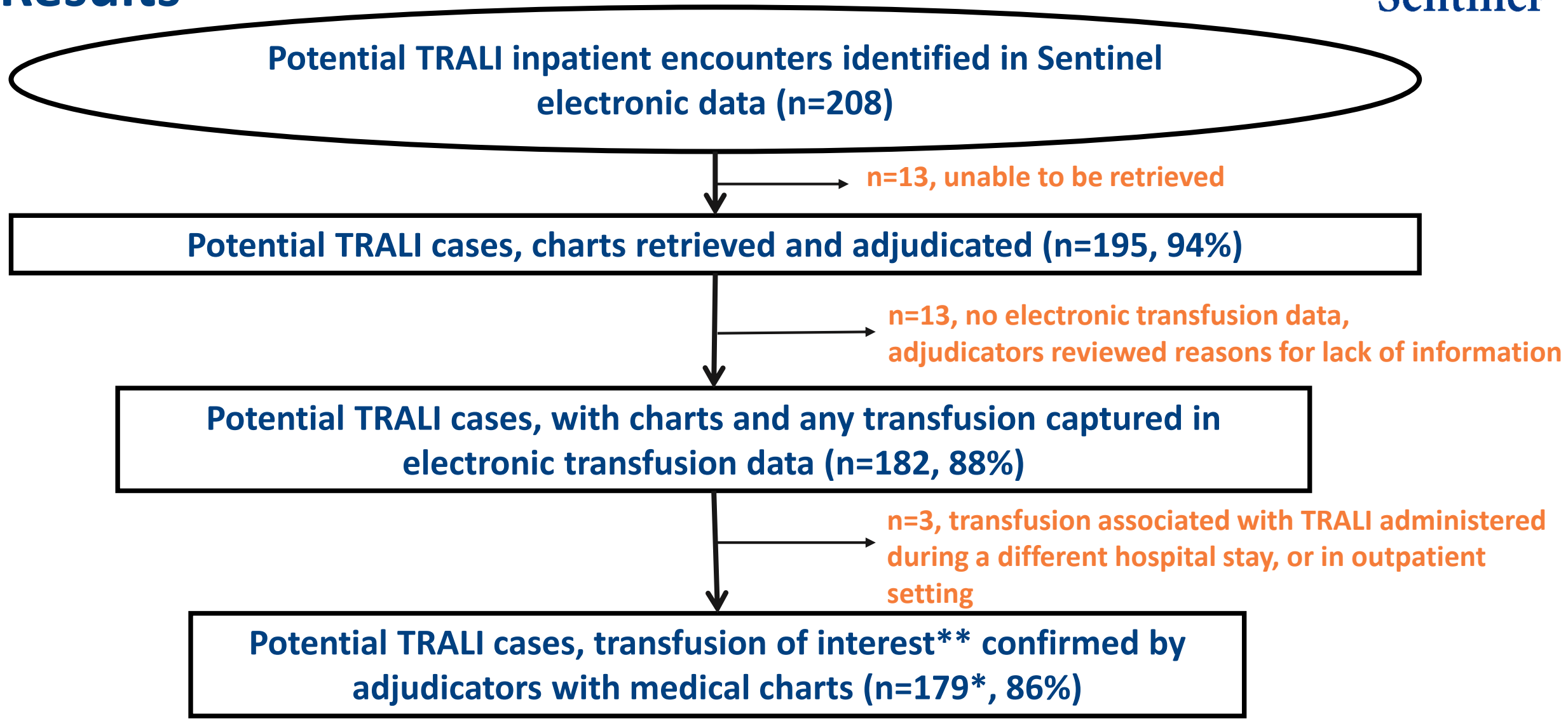
- Exploratory analyses:
  - We located TRALI cases with documentation of processing and collection methods in the medical charts.
  - In this subgroup, we quantified the PPV for processing/collection methods identified in the Sentinel electronic database as compared to medical charts
  - Gold standard: chart confirmed transfusion exposures
  - Limitation: few medical charts contained documentation of processing and collection methods

Results

- During the study period (September 2013-September 2015) there were almost 4 million inpatient stays in 169 hospitals and approximately 350,000 inpatient stays with transfusions

- Among 208 potential TRALI cases that were identified (all TRALI diagnosis codes)
  - Medical charts were available for 195 (94%) of these 208 potential cases

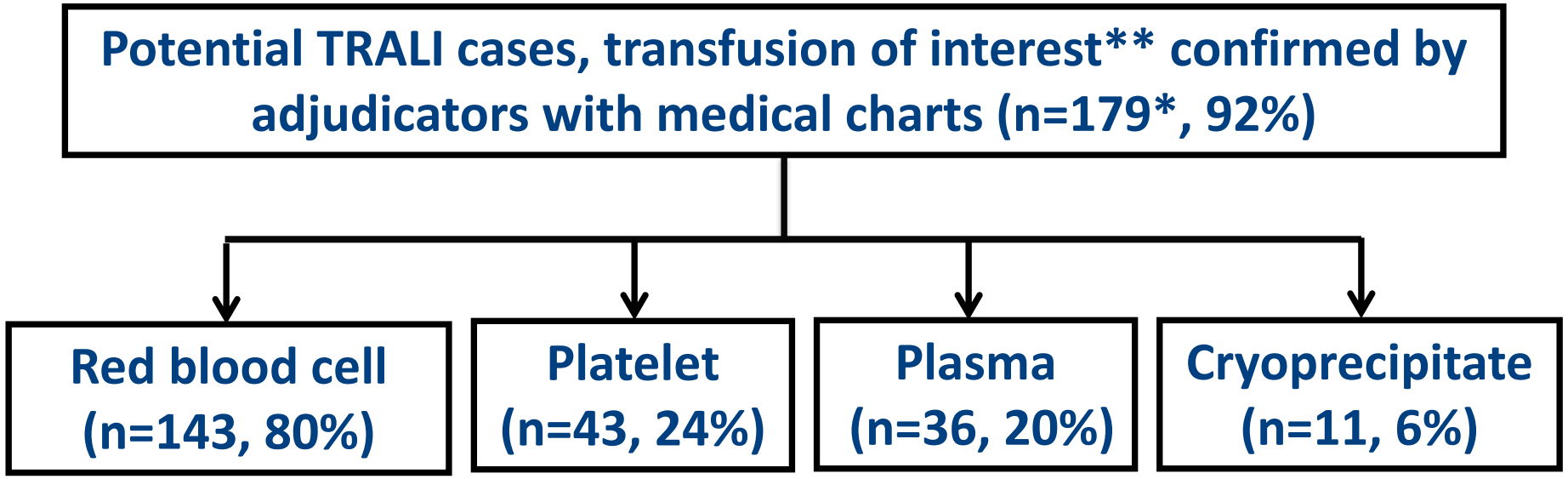
Results



**Gold standard - chart confirmed transfusion exposures*

***Transfusion of interest is transfusion potentially associated with TRALI*

Results



**Multiple blood components were often administered during a transfusion event*
*** Chart confirmed transfusions was gold standard for validation.*

Results

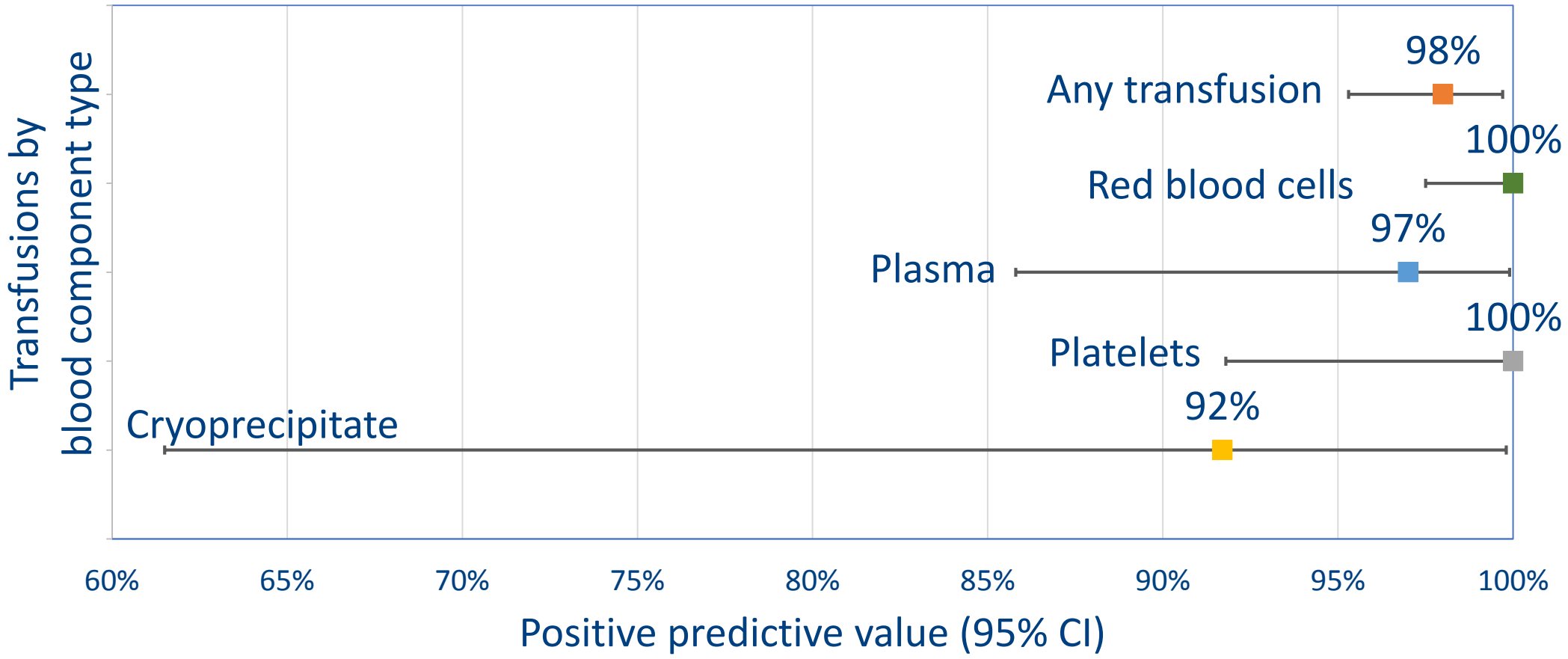
Transfusions by blood component and processing/collection method	Transfusions confirmed in charts** N	Transfusions recorded in Sentinel database N
Any transfusion*	179	182
Red blood cells	143	143
LR RBC	62	130
IR RBC	5	12
AP RBC	23	38
WB RBC	10	118
Plasma ¥	36	37
AP Plasma	4	10
WB Plasma	1	27
Platelets ¥	43	43
LR Platelets	15	38
IR Platelets	6	10
AP Platelets	16	39
Cryoprecipitate	11	12

**Multiple blood components were often administered during a transfusion event*

¥ No LR or IR plasma and WB platelet transfusions were documented in medical charts

*** Chart confirmed transfusions was gold standard for validation*

PPV analyses: Transfusion data in Sentinel database compared with transfusion information confirmed by the adjudicators*



*Gold standard - transfusion exposures confirmed with medical charts

Results – Main analyses

Leukocyte-reduced (LR) blood components in Sentinel electronic transfusion data vs. medical charts*			
Blood component	**Electronic transfusion data**	**Confirmed in Medical charts**	**PPV (95% CI)**
LR RBCs	130	62	47.7% (38.9%, 56.6%)
LR platelets	38	15	39.5% (24%, 56.6%)

*Gold standard - chart confirmed transfusion exposures

Results – Exploratory analyses

Leukocyte-reduced (LR) blood components in Sentinel electronic transfusion data vs. medical charts*			
Blood component	**Electronic transfusion data**	**Confirmed in Medical charts**	**PPV (95% CI)****
LR RBCs	62	62	100% (94.2%, 100%)
LR platelets	15	15	100% (78.2%, 100%)

*Gold standard - chart confirmed transfusion exposures

** Exploratory analyses compared electronic transfusion data with transfusions in charts only for cases in which adjudicators located processing/collection method in charts

Results – Main analyses

Irradiated (IR) blood components in Sentinel electronic transfusion data vs. medical charts*			
Blood component	**Electronic transfusion data**	**Confirmed in Medical charts**	**PPV (95% CI)**
IR RBCs	12	5	41.7% (15.2%, 72.3%)
IR platelets	10	6	60% (26.2%, 87.8%)

*Gold standard - PPV=100%, chart confirmed transfusion exposures

Results – Exploratory analyses

Irradiated blood components in Sentinel electronic transfusion data vs. medical charts*			
Blood component	**Electronic transfusion data**	**Confirmed in Medical charts**	**PPV (95% CI)****
IR RBCs	5	5	100% (47.8%, 100%)
IR platelets	6	6	100% (54.1%, 100%)

*Gold standard - PPV=100%, chart confirmed transfusion exposures

**Exploratory analyses compared electronic transfusion data with transfusions in charts only for cases in which adjudicators located processing/collection method in charts

Results – Main analyses

Apheresis derived (AP) blood components in electronic transfusion data vs. medical charts*			
Blood component	**Electronic transfusion data**	**Confirmed in Medical charts**	**PPV (95% CI)**
AP RBCs	38	23	60.5% (43.4%, 76%)
AP platelets	39	16	41% (25.6%, 57.9%)
AP plasma	10	4	40% (12.2%, 73.8%)

*Gold standard - PPV=100%, chart confirmed transfusion exposures

Results – Exploratory analyses

Apheresis derived (AP) blood components in electronic transfusion data vs. medical charts*			
Blood component	**Electronic transfusion data**	**Confirmed in Medical charts**	**PPV (95% CI)****
AP RBCs	23	23	100% (85.2%, 100%)
AP platelets	16	16	100% (79.4%, 100%)
AP plasma	4	4	100% (39.8%, 100%)

*Gold standard - chart confirmed transfusion exposures

**Exploratory analyses compared electronic transfusion data with transfusions in charts only for cases in which adjudicators located processing/collection method in charts

Results – Main analyses

Whole blood derived (WB) blood components in electronic transfusion data vs. medical charts*			
Blood component	**Electronic transfusion data**	**Confirmed in Medical charts**	**PPV (95% CI)**
WB RBCs	118	10	8.5% (4.1%, 15%)
WB plasma	27	1	3.7% (0.09%, 18.9%)

*Gold standard - PPV=100%, chart confirmed transfusion exposures

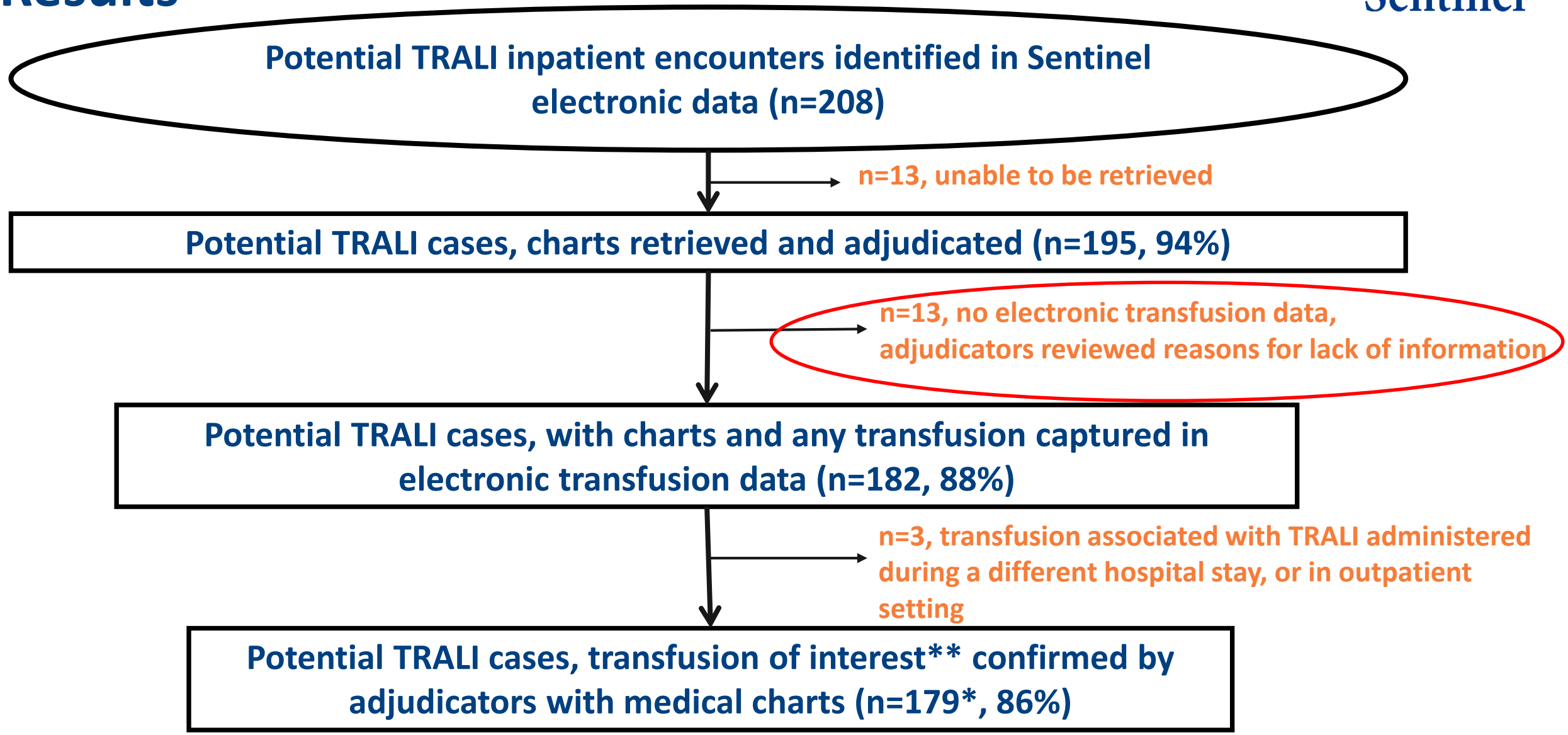
Results – Exploratory analyses

Whole blood derived components in electronic transfusion data vs. medical charts*			
Blood component	**Electronic transfusion data**	**Confirmed in Medical charts**	**PPV (95% CI)****
WB RBCs	10	10	100% (69.2%, 100%)
WB plasma	1	1	100% (2.5%, 100%)

*Gold standard - PPV=100%, chart confirmed transfusion exposures

**Exploratory analyses compared electronic transfusion data with transfusions in charts only for cases in which adjudicators located processing/collection method in charts

Results



**Gold standard- chart confirmed transfusion exposures*

***Transfusion of interest is transfusion potentially associated with TRALI*

Results

- Reasons transfusion not found in Sentinel inpatient electronic data but captured in a medical chart:
  - Transfusion occurred at a different facility so was noted in the chart but not in electronic data (e.g., transfer, outpatient, emergency department) (n=9)
  - Missing transfusion information (n=3)
  - No transfusion information was available in inpatient electronic data for one potential TRALI case but clinicians suspected intravenous immune globulin to be associated with TRALI (n=1)

Limitations of the study

- Only examined blood transfusions in potential TRALI cases
- Most transfusion codes in Sentinel inpatient electronic data were mapped to a blood component, but approximately 3% could not be mapped (n=6 of 182 potential TRALI cases)
  - Could be due to invalid coding or code not identified using current mapping system
- Only examined processing and collection methods in a subset of potential TRALI cases, as this information often was not available in charts, this limits conclusions that can be drawn

Current Limitations of Sentinel inpatient electronic data

- Limited information about medical conditions/events before/after a hospitalization
  - Rich information about care delivered during in-hospital stay

- Challenges with identifying temporal association between exposures and outcomes
  - Current Sentinel Common Data Model (SCDM) includes admission and discharge dates AND transfusion dates and times but no procedure or diagnosis dates and times
  - A data expansion effort is currently in progress to add these data elements to the SCDM

Conclusions

- Transfusions were well captured in Sentinel's inpatient electronic transfusion data
  - Included granular information about component type, which matched with medical charts (PPV >90%)
- Processing and collection methods were documented in Sentinel transfusion data but typically not available in charts
  - When processing and collection methods were documented in charts, we observed perfect concordance with electronic transfusion data, however sample sizes were limited
- This validation demonstrated the potential utility of Sentinel inpatient electronic data for future pharmacoepidemiology studies

Acknowledgements

- Sentinel Operations Center staff including Crystal Garcia
- Contributors in the U.S. Food and Drug Administration's Center for Biologics Evaluation and Research, Office of Biostatistics and Epidemiology
- Data Partner for providing inpatient data and expertise
- Clinical adjudicators at the Data Partner who conducted medical chart review

Optional Slides

Results – back up

Transfusion date and time match in charts compared to Sentinel inpatient data	
Transfusion date match	Median 0 (SD: 0.21, Min: -1, Max 1)
Transfusion time match	Median 0 minutes (SD 199, Min -1451, Max 1706) Median 0 hours (SD 3.3, Min -24, Max 28)

Sample ISBT-128 and Codabar codes

CODABAR		
Code	**Description**	**Prod_CDC**
18831	PLASMA IRRADIATED (from 250ml Whole Blood) (Storage -18 C or colder)	WBDPLASMA - Whole blood derived plasma
35772	AS-3 Red Blood Cells leukocyteS reduced^1 DIVIDED IRRADIATED (ACDA anticoagulant)(by pheresis)(P...	IRLRAPHRBC - Irradiated leukocyte reduced apheresis red blood cells
35773	AS-3 Red Blood Cells leukocyteS reduced^1 DIVIDED IRRADIATED (ACDA anticoagulant)(by pheresis)(P...	IRLRAPHRBC - Irradiated leukocyte reduced apheresis red blood cells

ISBT-128		
Code	**Description**	**Prod_CDC**
E0135	WHOLE BLOOD|Heparin/450mL/refg	WB - Whole blood
E1149	Thawed Apheresis FRESH FROZEN PLASMA|ACD-B/XX/refg	APHPLASMA - Apheresis plasma

Methods

- Study Population
  - Potential TRALI cases with electronic transfusion data were identified between September 2013-September 2015