

SENTINEL ASSESSMENT REPORT

PARENTERAL IRON AND ANAPHYLACTOID REACTIONS

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I. EXECUTIVE SUMMARY

A. OVERVIEW OF PROJECT

In May 2008, the U.S. Food and Drug Administration (FDA) launched the Sentinel Initiative, a long-term program designed to create a national electronic monitoring system for medical product safety (the Sentinel System).^{1,2} The Mini-Sentinel pilot was a collaborative effort between the FDA and a consortium of institutions, led by Harvard Pilgrim Healthcare Institute, to develop the scientific operations needed for the eventual Sentinel System. FDA chose to explore the relationship between parenteral iron products and anaphylaxis in the Mini-Sentinel environment based on concerns identified in the medical literature and post-marketing spontaneous adverse event reports. In addition, this project allowed Mini-Sentinel to test the use of an algorithm to identify cases of anaphylaxis using health plan administrative and claims data which Mini-Sentinel recently developed and validated.

The Summary Report of the Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium defines anaphylaxis as “a serious allergic reaction that is rapid in onset and may cause death.”³ Anaphylactoid reactions are immediate systemic reactions which mimic anaphylaxis but are caused by non-IgE-mediated release of mediators from mast cells and basophils.⁴ Clinically, anaphylaxis and anaphylactoid reactions appear identical, and treatment is the same for both. Parenteral iron is available as iron dextran, sodium ferric gluconate, iron sucrose, and ferumoxytol during the study period. The few available studies indicate parenteral iron use, particularly iron dextran, may be associated with anaphylaxis, but large studies are lacking. The objective of this study was to perform a one-time assessment of the association between iron dextran use and anaphylactoid/anaphylaxis reactions compared to other parenteral iron products. We will refer to these as anaphylaxis reactions throughout. Within the Mini-Sentinel Distributed Database including all current Data Partners, we identified a cohort of new parenteral iron users who were not on dialysis. We chose to exclude patients on dialysis because they had different prescribing patterns than other patients receiving parenteral iron, and because we considered them to be clinically different than other patients on parenteral iron. Among this cohort, we identified potential cases of anaphylaxis through: 1) an algorithm using diagnosis and procedure codes in the administrative health plan data of that we validated in a previous Mini-Sentinel project (criterion A, B, or C);⁵ patients meeting the criteria on the same day or day after administration of parenteral iron were identified; and 2) identification of patients who received epinephrine the same day as parenteral iron (criterion D), in order to improve the sensitivity of the algorithm. We conducted medical record review of cases of potential anaphylaxis. Two physician reviewers made judgments about whether anaphylaxis occurred using the Sampson Criteria.³ We calculated crude incidence rates of anaphylaxis among users of iron dextran and separately for users of other parenteral iron products. We determined Propensity scores (PS), which we used for two analytic approaches - matching and stratification. In matching, we estimated the odds ratio of anaphylaxis with the use of iron dextran vs other parenteral iron products among iron dextran users only. In stratification, we estimated the odds ratio of anaphylaxis with the use of iron dextran vs other parenteral iron products among both iron dextran users and other iron products users (in stratification). In PS stratification, we implemented trimming by PS percentiles to remove outliers with no comparable “controls” from the other exposure group.

B. SUMMARY OF FINDINGS

Among 70,866 new users, there were 24,603 iron dextran users and 46,263 users of the other parenteral iron products not on dialysis. Overall, 143 cases of potential anaphylaxis were identified using the electronic algorithm. This included 30 patients meeting the criteria of the validated Mini-Sentinel algorithm (criterion A, B, or C) and 121 patients who received epinephrine (criterion D). We sought charts for all potential cases and obtained 92 medical records for review. We confirmed 16 cases of anaphylaxis, with 8 among iron dextran users and 8 among users of other parenteral iron products. The PPV estimates were 60.0 (95% CI: 36.1-80.9) for the validated Mini-Sentinel algorithm and 10.4 (N=77; 95% CI: 4.6-19.4) for criterion D alone. The incidence of anaphylaxis in our new user cohort was 2 per 10,000 (95% CI: 1-4). Among iron dextran users the crude incidence rate for anaphylaxis was 4 per 10,000 (95% CI: 2-8) and among other iron product users (ferumoxytol, iron sucrose, sodium ferric gluconate) the crude incidence rate was 2 per 10,000 (95% CI 1-3). In crude analyses, the odds of anaphylaxis among iron dextran users was 2.3 (95% CI: 1-6) compared to other iron products users. In the PS matching analysis, for all sites, the odds of anaphylaxis for iron dextran users, compared to other parenteral iron users, was 8.001 (95% CI: 1.001-63.964; p-value 0.0499); this difference from the crude and stratified analysis may be due to confounding bias or to the rare prevalence of the outcome. We were unable to perform multiple logistic regression analysis due to the small number of anaphylaxis cases. For our analysis stratified by site and PS quintile, the odds of anaphylaxis for iron dextran new users, compared to non-dextran parenteral iron users was 2.74 (95% CI: 0.87-8.65; p-value 0.0859).

C. CONCLUSIONS

Our findings are consistent with those of Wang *et al.*, who found an odds of anaphylaxis among iron dextran users to be 2.6 (95% CI: 2.0-3.3) times that of non-dextrose parenteral iron users in a larger cohort of new users in non-dialysis patients from Medicare.⁶ Our validation efforts showed that restricting events to those occurred on the same or next day of IV Iron exposure did not improve the performance of the algorithm and the positive predictive value of the case definition based on an epinephrine dispensing alone on the same day as parenteral iron was low. On medical record review we found that several care centers routinely ordered epinephrine to the bedside when administering parenteral iron, accounting for the low specificity of epinephrine.

II. BACKGROUND AND OBJECTIVES

A. PATHOPHYSIOLOGY AND INCIDENCE OF ANAPHYLAXIS AND ANAPHYLACTOID REACTIONS

The Summary Report of the Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium defines anaphylaxis as “a serious allergic reaction that is rapid in onset and may cause death.”³ Anaphylactoid reactions are immediate systemic reactions which mimic anaphylaxis but are caused by non-IgE-mediated release of mediators from mast cells and basophils.⁴ They are also referred to as pseudoallergic drug reactions or non-allergic hypersensitivity reactions.⁷ Notably, hypersensitivity reactions to parenteral dextran therapy have been reported since the 1960s, and are attributed to dextran-reactive IgG antibodies.⁸ In general, symptoms of anaphylactoid reaction do not allow for discrimination between IgE-mediated anaphylaxis and non-IgE-mediated anaphylactoid reactions.⁹ Clinically, anaphylactoid reactions present and are treated identically to anaphylaxis.

Incidence rates of anaphylaxis reported in studies in U.S. populations vary greatly, ranging from approximately 10 to over 30 per 100,000 person-years.¹⁰⁻¹² Discrepancies may be related to differences

in the study populations, study design and case ascertainment methods, or the definition and criteria used to determine cases. Published studies have reported that approximately 11% to 17% of cases of anaphylaxis were attributed to administration of a medication, immunotherapy, or a diagnostic agent.¹⁰⁻¹² While the risk of anaphylaxis is not well-known for most medications, evaluation of spontaneous reports has led to Box Warnings for a number of medications (e.g. omalizumab, aproptinin, paclitaxel), as well as withdrawal of zomepirac sodium.¹³

B. EPIDEMIOLOGY OF IRON-INDUCED ANAPHYLAXIS/ANAPHYLACTOID REACTIONS

Parenteral iron is available as iron dextran, sodium ferric gluconate, iron sucrose, and ferumoxytol during this study period (Table 1). It is commonly used for the treatment of anemia in dialysis, malignancy, inflammatory bowel disease, and anemia due to ongoing blood losses (e.g., gastrointestinal bleeding, menorrhagia, postpartum bleeding). Few published studies have evaluated the risk of anaphylaxis associated with specific preparations of parenteral iron exposure.¹⁴⁻¹⁹ Only the iron dextran products (both low and high molecular weight) have a Box Warning regarding risk of anaphylactoid/anaphylaxis reactions and a test dose is recommended prior to parenteral administration of iron dextran.

Table 1. Parenteral iron products

Generic Name	Trade Name	Procedure Codes*	FDA Approval Date
Iron dextran	INFeD (low molecular weight), Dexferrum (high molecular weight), Cosmofer (low molecular weight)	J1750, J1751, J1752, J1760, J1770, J1780	Iron dextran-04/1957 INFeD-04/1974 Dexferrum-02/1996 Cosmofer-Not available in the U.S.
Sodium ferric gluconate	Ferrlecit	J2915, J2916, S0098	02/1999
Iron sucrose	Venofer	J1755, J1756	11/2000
Ferumoxytol	Feraheme	Non ESRD-Q0138, ESRD dialysis-Q0139	06/2009
Ferric carboxymaltose	Injectafer	J1439, Q9970	07/2013 (after end date for this study)

*HCPCS: Healthcare Common Procedure Coding System

In a review of adverse events reported to the FDA between 2001 and 2003, Chertow *et al.* described 1,141 reported events associated with parenteral iron use.¹⁵ The study authors commented that compared to low molecular weight iron, life-threatening adverse drug events were more frequent among those given high molecular weight iron. They also noted that adverse drug events were less common among those given iron sucrose and sodium ferric gluconate.

Fletes *et al.* in 2001 described parenteral iron dextran related adverse events in dialysis patients using data from Fresenius Medical Care clinical variance reports.¹⁶ The study included serious adverse drug events (e.g., dyspnea) and other adverse drug events (e.g., vomiting, flushing, and pruritus). Among the 165 reported adverse drug events, dyspnea, hypotension, and neurological symptoms were the most common serious symptoms. Twenty-six percent required emergency department evaluation, 11% required admission, and one patient died. Adverse drug events were 8 times more common among users of one brand of iron dextran, Dexferrum, compared to another (INFeD). The study estimated a rate of suspected adverse drug events at 20 per 100,000 doses.

Mamula *et al.* in 2002 described parenteral iron dextran related adverse events in children with inflammatory bowel disease in a single-site chart review study.¹⁷ From 1994 to 2000, among 70 patients who received 119 infusions, 10 patients had immediate hypersensitivity reactions. None were life-threatening and no patients were admitted; 3 had hypotension requiring epinephrine treatment.

Barton *et al.* in 2000 performed a study of 135 iron-deficient patients with normal renal function who failed oral iron therapy and were treated with iron dextran; the patients were premedicated with cimetidine, diphenhydramine, and dexamethasone. No patients had anaphylaxis; 13% had mild reactions, including arthralgias and myalgias.²⁰ Fishbane *et al.* in 1996 performed a study of 573 patients treated with iron dextran (INFeD) at four hemodialysis settings from 1993-1995; ten (1.7%) had anaphylactoid-type reactions.²¹

Auerbach *et al.* in 2004 described an open-label, multicenter prospective randomized trial in 157 anemic patients receiving chemotherapy, comparing subcutaneous erythropoietin to (1) no iron; (2) oral iron; (3) iron dextran repeated bolus; (4) iron dextran infusion.¹⁴ There were 3 patients in the infusion group with adverse events – two delayed myalgia/arthralgia, and one acute hypersensitivity (the hypersensitivity reaction was in a patient receiving a test dose of Dexferrum). Of the bolus patients, one experienced delayed myalgia/arthralgia, one experienced fatigue, and one reported shortness of breath. In the oral iron group, one patient experienced nausea. Auerbach also describes the use of rapidly administered (1 hour) 1 gram low molecular weight iron dextran in 396 iron deficient patients, in which there were no anaphylactoid reactions and no serious adverse events.²²

Michael *et al.* in 2002 compared drug intolerance between sodium ferric gluconate and iron dextran in a multicenter, crossover randomized, double blind, prospective study; the authors used placebo and historic controls. The authors found significantly less intolerance and serious adverse events in sodium ferric gluconate users compared to iron dextran controls.²³ Another study by Coyne *et al.* in 2003 investigated adverse reactions to sodium ferric gluconate in iron dextran sensitive and iron dextran tolerant patients as part of a double blind, prospective, controlled trial of sodium ferric gluconate safety and tolerability. In 143 dextran sensitive patients, three had suspected allergic reactions to sodium ferric gluconate, including one serious reaction. These reactions included one patient with back pain and doubling of Tryptase levels (indicating an allergic reaction), one flushing and doubling of Tryptase levels, and one with dyspnea, hypotension, wheezing, and high baseline Tryptase levels. Because the latter patient had a decline in Tryptase after the event, this serious reaction was considered non-allergic. There were 5 suspected allergic reactions in the 2,194 iron dextran tolerant patients, which included four reactions (2 pruritis, 1 chills, 1 dyspnea and chest pain) without a change in Tryptase levels that were classified as non-allergic and one patient with rash where levels were not obtained.²⁴

Moniem and Bhandari in 2007 performed a crossover study among dialysis patients to compare the safety and efficacy of CosmoFer (an iron dextran; 144 patients; 2,294 doses) and VenoFer (an iron sucrose; 110 patients; 2,111 doses).¹⁸ There were no anaphylaxis events in either group. In order to

compare the side effects and safety of low molecular weight iron dextran and iron sucrose, Sav *et al.* in 2007 recruited 30 patients in each group.¹⁹ All patients received a test dose before infusion. Eleven patients had an adverse reaction (including 1 with hypotension, no anaphylaxis) to iron dextran and 13 had an adverse reaction (including 2 cases with hypotension, no anaphylaxis) to iron sucrose. In another study comparing 979 doses of Cosmofer to 504 doses of Venofer, there were no cases of anaphylactoid-type reactions in either group.²⁵ In a chart review study of adverse events among 329 users of low molecular weight iron dextran and iron sucrose, one patient receiving iron sucrose had an adverse reaction, which consisted of generalized pruritis.²⁶

Although the non-dextran intravenous (IV) iron products appear to be safer, severe anaphylactic-type reactions have been reported with all approved IV Iron products in adverse events reported to the FDA.²⁷

A recent publication by Wang *et al.* of 688,183 new parenteral iron users in Medicare non-dialysis patients identified 444 anaphylaxis cases.⁶ The population included Medicare Part A and Part B fee-for service Medicare patients continuously enrolled for 12 months who received only one type of IV iron. The mean age of the population was 74 years old, and there were twice as many women as men. Most common indications for IV iron use were chronic kidney disease and GI or GU bleeding. The authors reported an adjusted odds ratio of 2.6 (95%CI, 2.0-3.3; p-value < .001) for anaphylaxis among new parenteral iron dextran users compared to non-dextrose iron products.

In a crossover study of 750 patients with chronic kidney disease not on dialysis who received ferumoxytol, one patient with a history of multiple drug allergies developed an anaphylactoid reaction and later recovered.²⁸ Similarly, a phase III trial of ferumoxytol or oral iron in 304 patients with chronic kidney disease patients found no hypotension or hypersensitivity in the ferumoxytol group.²⁹

C. VALIDITY OF ADMINISTRATIVE DATA TO IDENTIFY ANAPHYLAXIS

Few published studies have evaluated the validity of health plan administrative and claims data to identify anaphylaxis.^{10,11,30}

Bohlke *et al.* identified potential cases of anaphylaxis occurring between 1991 and 1997 in a population of children and adolescents enrolled in Group Health Cooperative, a health maintenance organization in Washington State and a Mini-Sentinel Data Partner.¹⁰ Investigators reviewed the medical charts of all potential cases identified using diagnosis codes specific for anaphylaxis (e.g. International Classification of Diseases, 9th Revision, Clinical Modification [ICD-9-CM] code 995.0, other anaphylactic shock; ICD-9-CM 995.6, anaphylactic shock caused by adverse food reaction) and a sample of cases identified with other nonspecific codes (e.g. ICD-9-CM, 995.3, allergy unspecified). Administrative and claims data from hospitalizations, emergency department visits, and outpatient encounters were assessed. The code with the highest positive predictive value (PPV) was ICD-9-CM 995.0, with 55% of potential cases confirmed to be a probable or possible case of anaphylaxis. The positive predictive values for nonspecific codes were much lower; for example, the positive predictive value for ICD-9-CM 995.3 (allergy unspecified) was 1%.

Johannes *et al.* evaluated the incidence of allergic reactions after exposure to antibiotics among members enrolled in a large U.S. health plan from July 2000 to June 2004.³⁰ For patients with an emergency department or hospitalization claim for anaphylaxis (ICD-9-CM 995.0), medical record review was conducted. Sixteen of 28 patients (57%) with this code were confirmed to have anaphylaxis.

Iribarren et al. evaluated the validity of ICD-9- CM code 995.0 among a cohort of patients diagnosed with asthma and a comparison group of patients without asthma enrolled in Kaiser Permanente Northern California (also a Mini-Sentinel Data Partner) between 1996 and 2006.¹¹ Administrative and claims data from hospitalizations, emergency department visits, and outpatient encounters were assessed. Medical record review was conducted and cases were confirmed based upon the *Summary Report of the Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium*.³ Of the 109 potential cases reviewed, 57 (52%) were confirmed as likely or probable cases.

The Mini-Sentinel Anaphylaxis Validation Workgroup developed and validated an algorithm consisting of diagnostic, symptom, and treatment codes in the Mini-Sentinel Distributed Database (MSDD).⁵ In a review of 122 patients for whom complete charts were received, 77 were judged by physician adjudicators to have anaphylaxis. The PPV for the algorithm was 63.1% (95% confidence interval [CI]: 53.9%-71.7%). The PPV was highest among inpatient visits with the ICD-9-CM codes 995.0 or 999.4.

None of these studies examined the use epinephrine on the same day as a drug product as a potential indicator of anaphylaxis.

D. VALIDITY OF ADMINISTRATIVE DATA TO IDENTIFY PARENTERAL IRON

An editorial in the New England Journal of Medicine by Auerbach and Rodgers in 2007 expressed concerns regarding potentially higher rates of adverse drug events among patients receiving high molecular weight iron dextran, and the difficulty of identifying high (Dexferrum) vs. low molecular weight iron dextran (INFeD) in claims data given the fact that both have the same billing code.³¹ Low molecular weight iron and the other iron products had lower rates of anaphylaxis according to the authors than high molecular weight iron. Unfortunately, administrative data does not indicate whether high or low molecular weight iron dextran is used. Medical records may contain information about what brand of parenteral iron was administered, but often contain only the generic drug name.

E. SUMMARY OF BACKGROUND

In summary, the epidemiology of parenteral iron-induced anaphylactoid or anaphylactic reactions is not well-described. There is limited information from a large comparative safety study about the risk of anaphylaxis between various IV Iron products, particularly in younger populations. Given the severity of the adverse drug reaction, and the potential difference in anaphylaxis among different products, a better understanding of the relative risk of anaphylaxis with use of iron dextran, compared to other iron products, is needed.

F. OBJECTIVE

The objective of this study was to perform a one-time assessment of the association between parenteral iron products and anaphylactoid/anaphylaxis reactions. The FDA and workgroup recognized the potential limitations of the study, such as the limited ability to differentiate between high and low molecular weight iron products (described in Section I), but believed the study would still produce useful information about the association in a large, diverse, population-based cohort. The results from this assessment were *not* expected to provide definitive evidence of a causal relation. We interpreted the results in the larger context of all that is known about the association from various sources, such as randomized controlled trials and post-market reports.

III. STUDY DESIGN AND METHODS

A. DATA SOURCE

In May 2008, the U.S. Food and Drug Administration (FDA) launched the Sentinel Initiative, a long-term program designed to create a national electronic monitoring system for medical product safety (the Sentinel System).^{1,2} The Mini-Sentinel pilot is a collaborative effort between the FDA and a consortium of institutions, led by Harvard Pilgrim Healthcare Institute, to develop the scientific operations needed for the eventual Sentinel System. Our assessment included all Mini-Sentinel Data Partners. Mini-Sentinel uses a distributed data approach in which Data Partners maintain physical and operational control over electronic data in their existing environments. Data Partners execute standardized programs provided by the Operations Center and then share the output of these programs, typically in summary form, with the Operations Center. Data Partners transform their data into the Mini-Sentinel Common Data Model format in order to standardize administrative and clinical information across Data Partners prior to running the SAS programs. The Mini-Sentinel Common Data Model is a standard data structure that allows Data Partners to quickly execute distributed programs against local data. The MSOC Data Core manages creation of the Mini-Sentinel Distributed Database using the MSCDM.

B. IDENTIFICATION OF NEW USERS OF DRUGS OF INTEREST

We used a “new-user” cohort design since the risk of anaphylaxis may be the highest at the first exposure.³² We identified health plan members with a first administration of a parenteral iron preparation during the period January 1, 2000 to June 30, 2013. Not all Data Partners had data available for the entire study period (Table 2). Use of parenteral iron preparations was identified using the procedure codes shown in Table 1. We did not identify parenteral iron administration using the National Drug Codes (NDCs), because in an earlier analysis we found the use of IV iron products identified by NDCs in the Mini-Sentinel Distributed Database to be quite low (~3,000 vs. ~200,000 identified by procedure codes. There could be duplication of patients identified with NDC and CPT codes, so that the same patient might be identified and included in the cohort more than once. In addition, procedure codes give more complete ascertainment of those receiving IV iron.

Table 2. Data availability by Data Partner (within the study timeframe)

Site ID	Available Data: First Date	Available Data: Last Date*
SITE 1	01/01/2008	06/30/2013
SITE 2	01/01/2006	05/30/2013
SITE 3	01/31/2004	06/30/2013
SITE 4	01/01/2000	04/30/2012
SITE 5	01/02/2000	12/31/2012
SITE 6	01/01/2000	12/31/2011
SITE 7	07/01/2004	05/30/2013
SITE 8	01/02/2000	06/30/2012

Site ID	Available Data: First Date	Available Data: Last Date*
SITE 9	01/02/2000	06/30/2012
SITE 10	06/01/2007	04/30/2013
SITE 11	01/01/2000	06/30/2013
SITE 12	01/01/2000	06/30/2013
SITE 13	01/01/2000	06/30/2013
SITE 14	01/01/2005	03/31/2013
SITE 15	01/31/2000	03/31/2013
SITE 16	01/31/2000	06/30/2013
SITE 17	01/01/2008	03/31/2013
SITE 18	01/01/2000	12/31/2012

*Some sites had data available beyond 06/30/2013, however, since we only used data through 06/30/2013 this is the date listed in this table.

We refer to the procedure date of the first administration of the iron preparation as the *index date*. We required eligible individuals to meet all of the following criteria during the 183-day period prior to the index date: 1) continuous health plan enrollment with pharmacy and medical benefits; and 2) no administration of any of the parenteral iron products of interest in the emergency department, outpatient setting, or inpatient visits; and (3) no procedure codes for dialysis (Appendix 1). Dialysis patients were excluded from analysis because in our feasibility study their prescribing patterns appeared different from other parenteral iron users and because dialysis patients may be clinically distinct from other parenteral iron users. Gaps of 45 days or less in enrollment were ignored because they usually represent administrative gaps rather than actual disenrollment.

The exposure group was new users of iron dextran. The comparison group was new users of other parenteral iron products (iron sucrose, ferumoxytol, and sodium ferric gluconate). We identified use of iron preparations in the inpatient, emergency department, and outpatient settings, although the majority of parenteral iron use was in the outpatient setting. For patients who were eligible for more than one new use episode during the study period, only their first eligible episode was included in the analysis.

C. IDENTIFICATION OF OUTCOME OF INTEREST

We employed the anaphylaxis algorithm (criterion A, B, or C) developed by the Mini-Sentinel Anaphylaxis Validation Workgroup to identify potential cases of anaphylaxis using health plan data (Appendices 2 and 3).⁵ We identified cases of potential anaphylaxis occurring on the day of or the day after exposure to parenteral iron. Because we expected that the number of cases identified would be small and we have planned to conduct the chart validation of those identified cases, we included a more sensitive algorithm that also identified patients who received epinephrine the same day as administered parenteral iron (criterion D). We reviewed these “epinephrine cases” using the same methods as potential anaphylaxis cases. During the validation, chart abstractors and adjudicators were blinded to

whether cases were identified using the validated Mini-Sentinel anaphylaxis algorithm or from epinephrine administration.

D. CHART REVIEW VALIDATION OF CASES OF POTENTIAL ANAPHYLAXIS

The chart review followed an approach modified from the previous Mini-Sentinel validation studies,^{5,33} including: (1) identification of a clinical definition for anaphylaxis for use with medical records data; (2) identification, retrieval, and de-identification of medical records of patients who have been identified by Data Partners utilizing the anaphylaxis algorithm (Table 3); (3) chart abstraction by a trained abstractor using a structured abstraction form; and (4) adjudication of anaphylaxis cases based on physician review of the completed data abstraction forms. In addition, we recorded pre-medications (diphenhydramine, acetaminophen, or steroid) administered before parenteral iron as noted in the medical record, and we abstracted the generic and brand names for each parenteral iron product used, if noted in the medical record.

Table 3. Clinical criteria for diagnosing anaphylaxis for use in primary analysis³

Anaphylaxis is Highly Likely When Any of the Following 3 Criteria Are Fulfilled:
<p>1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING:</p> <ul style="list-style-type: none"> a. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia) b. Reduced blood pressure or associated symptoms of end-organ dysfunction (e.g., hypotonia [collapse], syncope, incontinence)
<p>2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours):</p> <ul style="list-style-type: none"> a. Involvement of the skin-mucosal tissue (e.g., generalized hives, itch-flush, swollen lips-tongue uvula) b. Respiratory compromise (e.g., dyspnea, wheeze-bronchospasm, stridor, reduced peak expiratory flow, hypoxemia) c. Reduced blood pressure or associated symptoms (e.g., hypotonia [collapse], syncope, incontinence) d. Persistent gastrointestinal symptoms (e.g., crampy abdominal pain, vomiting)
<p>3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours):</p> <ul style="list-style-type: none"> a. Infants and children: low systolic blood pressure (age specific) or greater than 30% decrease in systolic blood pressure* b. Adults: systolic blood pressure of less than 90 mm Hg or greater than 30% decrease from that person's baseline blood pressure
<p>*Low systolic blood pressure for children is defined as less than 70 mm Hg from 1 month to 1 year, less than (70 mm Hg + [2 x age]) from 1 to 10 years, and less than 90 mm Hg from 11 to 17 years.</p>

We requested all relevant portions of the medical record from all participating Data Partners with cases of interest for which charts were eligible for retrieval, in keeping with the minimum necessary standard. We were able to obtain 92 of the 143 (64%) medical records requested (Figure 1). The record was redacted, abstracted, and reviewed. Abstraction was performed by three experienced medical record abstractors who were trained nurses or physicians. We trained the abstractors using a two-step process: first they participated in a telephone-based introduction to the study methods and they later all reviewed the same ten charts and compared results. Because their reviews were consistent and thorough, they then reviewed the remaining charts. The number of potential anaphylaxis cases was relatively small so the goal was to validate all potential cases. Two physicians reviewed abstracted information and made judgments about whether anaphylaxis occurred. They used the clinical definition developed by a recent consensus group and published by Sampson *et al.* as the gold standard for determining whether anaphylaxis occurred.³ Only events classified as cases of anaphylaxis, determined based on the clinical definition developed by Sampson *et al.* were used in the primary analysis (Table 3). The physician reviewers and chart abstractors were blinded to whether cases were identified using the validated Mini-Sentinel anaphylaxis algorithm or from epinephrine administration, as well as to study objectives and hypothesis.

For the secondary analyses, clinician adjudicators made judgments about whether all potential cases were (1) not a hypersensitivity reaction; (2) mild hypersensitivity; (3) moderate hypersensitivity; or (4) severe hypersensitivity, using the classification system developed by Brown *et al.* in 2004 (Table 4).³⁴ We used moderate and severe allergic reactions as a separate outcome variable in the secondary analysis.

Table 4. Grading system for generalized hypersensitivity reactions for use in secondary analysis³⁴

Grade	Defined by
1 – Mild (skin and subcutaneous tissues only)*	Generalized erythema, urticaria, periorbital edema, or angioedema
2 – Moderate (features suggesting respiratory, cardiovascular, or gastrointestinal involvement)	Dyspnea, stridor, wheeze, nausea, vomiting, dizziness, or abdominal pain
3 – Severe (hypoxia, hypotension, or neurologic compromise)	Cyanosis or SpO ₂ ≤ 92% at any stage, hypotension (systolic blood pressure < 90 mm Hg in adults), confusion, collapse, loss of consciousness, or incontinence
*Mild reactions can be further sub classified into those with and without angioedema (see text).	

E. IDENTIFICATION OF COVARIATES

Table 5 lists the covariates we identified in the 183-day period preceding (and including) the index date identified from the MSDD. Age on index date and gender was identified from the MSDD’s demographic files. Diagnostic codes recorded during inpatient, outpatient, or emergency department encounters were obtained from the MSDD’s diagnosis file. Medications were identified using NDC and HCPCS codes.

Table 5. ICD-9-CM codes to identify covariates

Confounder	Categorization	Identified by ICD-9-CM Code(s) (unless otherwise noted)
History of anaphylaxis, not related to food*	Yes/No	995.0, 999.4, V13.81
Drug allergy*	Yes/No	995.27, V15.08, V14
Atopic dermatitis	Yes/No	691.8
Food/insect/latex allergy*	Yes/No	V15.01, V15.02, V15.03, V15.04, V15.05, V15.06, 995.6, V15.07
Other allergy*	Yes/No	995.3, 518.6, 558.3, 708, V15.09
Allergic rhinitis	Yes/No	477
Asthma	Yes/No	493
Chronic obstructive pulmonary disease (COPD)	Yes/No	491, 492, 496
Coronary heart disease	Yes/No	413, 414
Primary hypertension	Yes/No	401
HIV infection	Yes/No	V08, 042
Immunosuppressive therapy	Yes/No	Outpatient pharmacy dispensing file using National Drug Codes and procedure file for identifying HCPCs codes for selected immunosuppressives (alefacept, azathioprine, basiliximab, belatacept, non-ophthalmic cyclosporine, glatiramer, mycophenolate, sirolimus, and non-topical tacrolimus), selected immunomodulators (abatacept, adalumumab, anakinra, canakinumab, certolizumab, dimethyl fumarate, etanercept, fingolimod, golimumab, infliximab, lenalidomide, mitoxantrone, natalizumab, pomalidomide, rilonacept, teriflunomide, thalidomide, tocilizumab, and ustekinumab), a selected antirheumatic kinase inhibitor (tofacitinib), selected monoclonal antibodies (alemtuzumab, ofatumumab, and rituximab), or an alkylating agent (cyclophosphamide)
Oral steroid use* [†]	Yes/No	Outpatient pharmacy dispensing file using National

Confounder	Categorization	Identified by ICD-9-CM Code(s) (unless otherwise noted)
		Drug Codes
Injectable steroid use* [†]	Yes/No	Outpatient pharmacy dispensing file using National Drug Codes and procedure file for identifying HCPCS codes
Antibiotic use [†]	Yes/No	Outpatient pharmacy dispensing file using National Drug Codes
Beta blocker use [†]	Yes/No	Outpatient pharmacy dispensing file using National Drug Codes
ACE inhibitor use [†]	Yes/No	Outpatient pharmacy dispensing file using National Drug Codes
ARB use [†]	Yes/No	Outpatient pharmacy dispensing file using National Drug Codes
Year of new use	Number	n/a
Clinical setting where IV iron administered	Inpatient, Outpatient, Emergency Department	n/a
<p>*For history of anaphylaxis not related to food, oral steroid use, injectable steroid use, drug allergy, other allergy, food/insect/latex allergy identify codes found within 183 days preceding the index date, but not including the index date.</p> <p>[†]Use defined as a dispensing (fill) in the outpatient pharmacy dispensing file for 183 days preceding and including the index date</p>		

F. FOLLOW-UP

Follow up began on the index date, and ended on the first occurrence of anaphylaxis or one day after the index date, whichever occurred first. Only the first eligible episode was included in the analysis.

G. ANALYSIS

1. Exclusion of sites with zero outcome events or use of only one iron product

We excluded Data Partner sites that had no anaphylactic events, after medical record review, from the inferential analysis. Because our final outcome was a risk ratio rather than a risk difference and because all analyses were stratified on site, Data Partner sites with zero outcome events would contribute no data to the relative risk analysis. We believed the bias introduced by combining sites with different prescribing and coding practices and treating them as a single site to be potentially significant. Similarly, sites which use only one parenteral iron product were excluded from the inferential analysis.

2. Exclusion of additional sites

We excluded one Data Partner which was unable to obtain medical records and we excluded patients over 65 years old from one Data Partner because we were also unable to obtain their medical records.

3. Comparison of baseline characteristics

We compared the baseline characteristics between new users of iron dextran and new users of other iron products, overall and at each Data Partner (See section: Results, Patient Demographics). We used standardized differences, which is less sensitive to sample size than p-values in t-tests or Chi-square tests, for the comparisons. A value of 0.1 or greater indicates meaningful covariate imbalance.²⁵

4. Calculation of incidence

We calculated the incidence of anaphylaxis for new users of iron dextran and new users of other parenteral iron, with 95% CIs. We calculated the overall incidence across all IV iron products for all sites and stratified by site.

5. Indications of use

We identified one or more indications for the use of parenteral iron for each patient (Table 6), using ICD-9-CM codes in the MSDD diagnosis file during 183 days prior to (and including) the index date. We allowed patients to have more than one potential indication. For those patients receiving parenteral iron who did not have any of these diagnostic codes, we categorized as “other indication”. For patients categorized as “other indication”, we obtained a list of all diagnostic codes within 7 days prior to the index date. Diagnostic codes for patients with “other indication” were compiled for descriptive purposes only.

Table 6. Potential indications for prescription of parenteral iron

Diagnosis	Identified by ICD-9-CM Code(s)
Anemia complicating pregnancy, childbirth or the puerperium	648.20-648.24
Anemia in chronic kidney disease	285.21
Intestinal malabsorption, including celiac disease	579
Chronic iron deficiency anemia secondary to blood loss (chronic); Iron deficiency anemia	280
Chronic kidney disease (stages 3-5)	585.3, 585.4, 585.5
Chemotherapy encounter	V58.11, V07.39
Chemotherapy induced anemia, cancer induced anemia	285.3, 285.22
Endometriosis	617
Esophageal cancer	150, 230.1
Esophageal varices	456.0, 456.1, 456.2

Diagnosis	
Peptic ulcer disease	531, 532, 533, 534
Intestinal cancer	152, 153, 159.0, 230.3, 230.7
Menorrhagia	626.2
Ulcerative colitis; Crohn's disease	556, 555
Uterine fibroid	654.1, 218
Stomach cancer	151, 230.2
Other	None of the above

6. Analysis comparing the risk of anaphylaxis between parenteral iron dextran and other parenteral iron products

a. Estimation of relative risk

We employed two propensity score-based approaches – matching³⁵ and stratification³⁶ – to investigate the association between the use of iron dextran and anaphylaxis, with use of other parenteral iron products as the comparison group. The propensity score was defined as the probability of receiving iron dextran given the measured confounders. We used the propensity score methods as our primary approach because the number of anaphylaxis events was small and the number of confounders was relatively large. The propensity score approach overcomes this issue by allowing us to adjust for all measured confounders simultaneously through a composite summary score.³⁶ We estimated the propensity scores by site using a logistic model common to all Data Partners using the probability of receiving iron dextran as the dependent variable and covariates in Table 5 as independent variables. Each site had its own model fitting and associated model estimates, although the form of the model was the same.

Propensity score matching was conducted within sites. We matched one iron dextran user with one other iron product user using 1:1 nearest-neighbor matching without replacement with a caliper of 0.05.³⁷ Unmatched patients were excluded from subsequent analyses. Each Data Partner transferred an aggregated dataset of the matched cohort (with matched pairs linked to each other), which included only the number of users and outcome events in each treatment group, to the project team. The project team then estimated the odds ratio of the confirmed anaphylactoid/anaphylaxis event, from the Sampson criteria, with the use of iron dextran vs. other iron products by fitting an unconditional logistic regression model to the matched population. The aggregated dataset only included the number of users and outcome events within each treatment group. By matching one iron dextran user with one other iron product user with similar propensity score, we estimated the average treatment effect among the treated (ATT). Thus, we also performed propensity score stratification to estimate the population-wide average treatment effect (ATE).

In propensity score stratification, each Data Partner divided its entire study population (iron dextran users and other iron products users) into 5 strata based on the site-specific propensity score quintiles.

Each Data Partner transferred an aggregated dataset consisting of the within-stratum numbers users and anaphylaxis events in each treatment group. The project team fit a stratified logistic regression model on the probability of anaphylaxis comparing the exposure groups (iron dextran vs. other iron products) stratifying both on site and within-site propensity score strata. The results from the propensity score matching and stratification analyses could differ if the effect of iron dextran differs among the subgroup of actual iron dextran users (ATT) versus among the entire group of all parenteral iron products users (ATE). In the analyses, we discovered that the PS distributions among iron dextran users and other iron products users overlap poorly at some sites. In consequence, we performed sensitivity analyses by trimming the study population at the 1st and 99th percentiles and the 2.5th and 97.5th percentiles of the PS distributions among the iron dextran users and the other iron products users respectively.³⁸ We then re-fit the stratified logistic regression model among the trimmed populations to calculate the ORs and 95% CIs.

7. Secondary analyses

a. Multivariable-adjusted outcome logistic regression analysis

Due to the small number of anaphylaxis cases, we were unable to perform multivariable-adjusted outcome logistic regression analysis. |

b. Moderate and severe hypersensitivity reactions

Moderate and severe hypersensitivity reactions, adjudicated using methods in Brown's study, were combined as a single outcome variable in a secondary analysis.³⁴ We then analyzed the risk of a moderate or severe hypersensitivity reaction among iron dextran users compared to other parenteral iron users, as described above.

c. Premedication

The questions was raised in responses to the feasibility report regarding whether premedication is related to the symptoms of an anaphylaxis in parenteral iron use, we determined the number and percent of confirmed cases of anaphylaxis which received premedication for each parenteral iron product.

d. Brand name drugs

In order to understand whether high molecular weight (Dexferrum) or low molecular weight (INFeD) iron dextran is associated with anaphylaxis, we abstracted from each medical record the brand name of parenteral iron used.

e. Positive predictive value of anaphylaxis algorithm

We determined the positive predictive value (PPV) of the validated Mini-Sentinel anaphylaxis algorithm (Criterion A, B, or C) for detecting anaphylaxis among IV iron users by dividing the total number of confirmed cases by the total number of cases detected using the algorithm. We also determined the PPV for Criterion A, B, C, and D (D = administration of epinephrine) separately.

8. Sample size calculation

From the feasibility assessment results, we estimated that there were 40,015 new iron dextran users and 60,714 new users of other iron products who did not have a diagnostic code for dialysis in the previous 183 days. We varied the baseline risks of anaphylaxis and epinephrine administration according

to the modular program results, and computed the least detectable relative risk at a 0.05 significance level with a power of approximately 80% using the Fischer’s Exact Test. In our power calculation, we used the relative risk instead of odds ratio because the outcome variable is rare. Given the incidence of this rare outcome, the results of these approaches are identical to at least 2 decimal places (Table 7).

The workgroup determined that a study with enough power to detect a relative risk of 4 was adequate to perform a protocol-based assessment. FDA determined that, given the rarity and severity of the outcome (anaphylaxis), a relative risk of four or higher would be enough to influence policy decisions. Because our least detectable relative risks are all smaller than 4, the study has sufficient sample size for the primary objective.

Table 7. Sample size power calculations

Baseline Risk per 10,000 Patients	Relative Risk	Power
2.05	2.80	81.3%
2.15	2.70	79.6%
2.25	2.70	81.5%
2.35	2.60	79.3%
2.45	2.60	81.1%
2.55	2.55	80.7%
2.65	2.50	80.2%
7.50	1.80	80.8%
8.00	1.75	78.9%
8.50	1.75	81.4%
9.00	1.70	78.9%
9.50	1.70	81.1%

IV. RESULTS

A. NUMBER OF USERS

In the MSDD from January 1, 2000 to June 30, 2013, there were 77,057,767 patients enrolled (at least one day) and 98,262 new parenteral iron product users. The incidence of new parenteral iron product

use in this population was 1.28 per 1000 patients. Among patients who did not have codes indicating dialysis use (Appendix 1), there were 74,948 new users. Iron dextran use was more common in non-dialysis patients than dialysis patients (36% among non-dialysis patients administered parenteral iron compared to 2.5% among dialysis patients). Among new users, iron sucrose was the most common parenteral iron product used overall (47%), although use of iron sucrose was much more common in dialysis patients (70% of new parenteral iron users used iron sucrose) than non-dialysis patients (40% of new parenteral iron users used iron sucrose).

B. PATIENT DEMOGRAPHICS

In our population of new parenteral iron users who were not on dialysis, 74% were female and more than half were aged 20-64 years. Use of parenteral iron products increased from 272 users in the year 2000 to 12,615 users in 2012 due to the years of availability of data, with more Data Partners having data available in more recent years. Ninety five percent of patients received parenteral iron in the outpatient setting (Table 8).

Table 8. Baseline characteristics of new users (not on dialysis) according to parenteral iron product administered [from MSDD]

Characteristic		Total Sample		Iron Dextran		Ferric Gluconate		Iron Sucrose		Ferumoxylol	
		n	%	n	% [†]	n	% [†]	n	% [†]	n	% [†]
Number of patients		74,948	100.0	26,606	100.0	10,919	100.0	29,781	100.0	7,642	100.0
Age on index date	0-10 years	121	0.2	43	0.2	29	0.3	49	0.2	0	0.0
	11-19 years	839	1.1	344	1.3	107	1.0	361	1.2	27	0.4
	20-64 years	44,737	59.7	17,637	66.3	7,063	64.7	16,623	55.8	3,414	44.7
	65 and older	29,251	39.0	8,582	32.3	3,720	34.1	12,748	42.8	4,201	55.0
Gender	Female	55,454	74.0	20,829	78.3	8,072	73.9	21,422	71.9	5,131	67.1
	Male	19,482	26.0	5,774	21.7	2,842	26.0	8,356	28.1	2,510	32.8
History of:	Anaphylaxis, not related to food**	56	0.1	18	0.1	9	0.1	25	0.1	4	0.1
	Drug allergy	1,986	2.6	710	2.7	261	2.4	764	2.6	251	3.3
	Atopic dermatitis	386	0.5	144	0.5	60	0.6	142	0.5	40	0.5
	Food, latex, insect bite allergy	168	0.2	54	0.2	29	0.3	69	0.2	16	0.2
	Other allergy	1,138	1.5	456	1.7	173	1.6	408	1.4	101	1.3
	Allergic rhinitis	4,487	6.0	1,753	6.6	623	5.7	1,630	5.5	481	6.3
	Asthma	6,419	8.6	2,240	8.4	994	9.1	2,575	8.7	610	8.0
	COPD	9,461	12.6	2,996	11.3	1,314	12.03	4,022	13.5	1,129	14.8
	Coronary heart disease	14,345	19.1	3,925	14.8	1,916	17.91	6,588	22.1	1,916	25.1

Characteristic		Total Sample		Iron Dextran		Ferric Gluconate		Iron Sucrose		Ferumoxytol	
		n	%	n	% [†]	n	% [†]	n	% [†]	n	% [†]
	Hypertension	38,266	51.0	11,781	44.3	5,188	47.5	16,408	55.1	4,849	63.5
	HIV infection	219	0.3	74	0.3	45	0.4	77	0.3	23	0.3
Current use of:	Immunosuppressive therapy	4,099	5.5	1,247	4.7	655	6.0	1,763	5.9	434	5.7
	Oral steroid use	13,175	17.6	4,577	17.2	1,978	18.1	5,224	17.5	1,396	18.3
	Injectable steroid	13,149	17.5	4,837	18.2	1,921	17.6	4,816	16.2	1,575	20.6
	Antibiotic	36,714	49.0	13,258	49.8	5,530	50.7	14,266	47.9	3,660	47.9
	Beta blocker	19,801	26.4	5,909	22.2	2,716	24.9	8,657	29.1	2,519	33.0
	ACE inhibitor	16,384	21.9	5,556	20.9	2,170	19.9	6,700	22.5	1,958	25.6
	ARB	8,883	11.9	2,644	9.9	1,187	10.9	3,880	13.0	1,172	15.3
Year of new use	2000	272	0.4	272	1.0	0	0.0	0	0.0	0	0.0
	2001	654	0.9	631	2.4	20	0.2	2	0.01	1	0.01
	2002	700	0.9	655	2.5	35	0.3	10	0.03	0	0.0
	2003	898	1.2	748	2.8	91	0.8	59	0.2	0	0.0
	2004	1,261	1.7	892	3.4	223	2.0	146	0.5	0	0.0
	2005	1,451	1.9	849	3.2	371	3.4	231	0.8	0	0.0
	2006	2,828	3.8	1,401	5.3	584	5.4	843	2.8	0	0.0
	2007	4,695	6.3	2,058	7.7	886	8.1	1,751	5.9	0	0.0
	2008	7,616	10.2	2,229	8.4	1,583	14.5	3,804	12.8	0	0.0
	2009	12,041	16.1	4,325	16.3	2,103	19.3	5,612	18.8	1	0.0

Characteristic		Total Sample		Iron Dextran		Ferric Gluconate		Iron Sucrose		Ferumoxylol	
		n	%	n	% [†]	n	% [†]	n	% [†]	n	% [†]
	2010	12,206	16.3	3,949	14.8	1,492	13.7	5,059	17.0	1,706	22.3
	2011	12,521	16.7	3,756	14.1	1,421	13.0	5,064	17.0	2,280	29.8
	2012	12,615	16.8	3,442	12.9	1,479	13.6	5,113	17.2	2,581	33.8
	2013	5,190	6.9	1,399	5.3	631	5.8	2,087	7.0	1,073	14.0
Clinical setting (where IV iron administered)	Outpatient	70,870	94.6	26,165	98.3	9,587	87.8	27,539	92.5	7,579	99.2
	Inpatient	3,001	4.0	305	1.1	1,078	9.9	1,578	5.3	40	0.5
	Emergency department	1,081	1.4	138	0.5	254	2.3	666	2.2	23	0.3
<p>**Anaphylaxis history should be found within 183 days preceding (BUT NOT INCLUDING) the index date</p> <p>%[†] within each treatment group</p>											

1. Medical records obtained and algorithm PPV

Our algorithm (criteria A, B, C, and D) identified 143 potential cases of anaphylaxis on the same day as parenteral iron administration and four potential cases of anaphylaxis on the day after iron dextran administration (Table 9). We were able to obtain 92 of the 143 (64%) medical records requested (Figure 1). Of the 92 charts obtained, 42 included outpatient records, 22 emergency department records, and 54 inpatient records. The number of charts obtained varied from 50-100% across Data Partners. Of those charts obtained, the number of chart components we requested which were provided varied. For example, all ED records, 96% of inpatient records, and 79% of outpatient records contained clinician notes.(Table 10) The median chart length was 26 pages (range 1-596 pages).

Table 9. New parenteral iron users (not on dialysis) meeting criteria for identification of potential cases of anaphylaxis, 2000-June 2013 from MSDD

Inclusion Criteria Met	Same Day as Parenteral Iron Administration (MSDD)	Day After Parenteral Iron Administration (MSDD)	Charts Obtained	Cases Anaphylaxis Confirmed
	n	n	n	n
Criterion A	18	4	12	6
Criterion B	7	0	4	4
Criterion C	9	0	5	3
Criterion A, B or C	30	4	20	12
Criterion D	121	N/A*	77	8
Criterion A, B, C or D	143	N/A	92	16

*We did not attempt to obtain medical records for patients receiving epinephrine the day after parenteral iron (Criterion D) because we did not expect this to yield any additional anaphylaxis cases

Figure 1. Number and percent of medical records requested and obtained by Data Partner

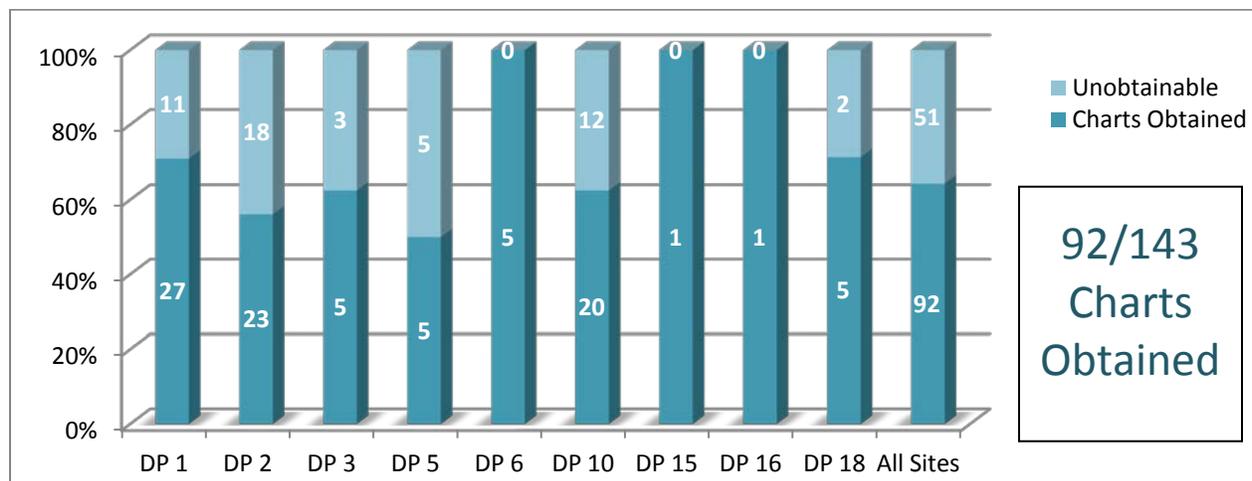


Table 10. Available components among charts received*

Chart Characteristic	n	%
Total Charts Received	92	100.0
Outpatient: Total Potential Cases	42	45.7
	42	45.7
Records with the requested components		
Clinician notes	33	78.6
EMT notes	3	7.1
All vital signs	29	69.0
All orders	35	83.3
Medication administration record	33	78.6
Allergy list	23	54.8
Outpatient allergist notes >30 days	1	2.4
Inpatient: Total Potential Cases	54	58.7
Records with the requested components		
Physician notes	52	96.3
All orders	42	77.8
Nursing medication administration record	36	66.7
All vital signs	40	74.1
Allergy list	37	68.5
Transfer note	2	3.7
Copies of all items in ER list	9	16.7
Emergency Department: Total Potential Cases	22	23.9
Records with the requested components		
ER notes	22	100.0
EMT notes	2	9.1
All orders	19	86.4
Nursing medication administration record	16	72.7
All vital signs	22	100.0
Allergy list	18	81.8
Transfer note	4	18.2

*Includes information on all charts received. Total encounter types sum to more than the total patients sampled since Data Partners may have requested more than one medical record for the encounter date of interest.

Physician reviewers identified 16 confirmed cases of anaphylaxis, were unable to confirm one case of anaphylaxis based on the medical record (this one case not included in analysis), and determined that 75 cases were not anaphylaxis. Table 11 shows the PPV estimates overall and for each of the specific criterion.

Table 11. Event classification by inclusion criteria*

Specific Criteria*	# Cases Anaphylaxis Confirmed	# Cases Anaphylaxis Not Confirmed	# of Charts Obtained	PPV (%)	95% Confidence Interval
Criteria A	6	6	12	50.0	21.1-78.9
Criteria B	4	0	4	100.0	40.0-100.0
Criteria C	3	2	5	60.0	14.7-94.7
Criterion A, B, and C	12	8	20	60.0	36.1-80.9
Criteria D	8	68	77	10.4	4.6-19.4

*Inclusion criteria are not mutually exclusive

In order to better understand the low PPV of the epinephrine patients, we re-reviewed medical records for these patients. We found that several patients had IV iron ordered on an order set which included routine orders for epinephrine to the bedside. This generated epinephrine orders even when it was not administered.

2. Potential indications for administration of parenteral iron

The most common diagnoses associated an indication for parenteral iron that we identified was chronic iron deficiency anemia, in 81% patients. Twenty percent of our new users cohort, after exclusion of those who have codes for dialysis, had diagnostic codes for chronic kidney disease. Eight percent had codes for intestinal malabsorption and 7% for chemotherapy. Eight percent of our study population did not have any of the diagnostic codes listed in Table 12.

Table 12. Potential indications for new parenteral iron users (not on dialysis), 2000-2012 from MSDD

Indication	All Products		Iron Dextran Users		Ferric Gluconate Users		Iron Sucrose Users		Ferumoxytol Users	
	n	% [†]	n	% [†]	n	% [†]	n	% [†]	n	% [†]
Total Users	74,948	100.0	26,606	100.0	10,919	100.0	29,781	100.0	7,642	100.0
Chronic iron deficiency anemia secondary to blood loss; Iron deficiency anemia	60,476	80.7	21,993	82.7	8,558	78.4	23,320	78.3	6,605	86.4
Chronic kidney disease	14,941	19.9	2,031	7.6	1,508	13.8	8,366	28.1	3,036	39.7
Anemia in chronic kidney disease	11,341	15.1	1,728	6.5	1,135	10.4	6,340	21.3	2,138	28.0
Intestinal malabsorption (incl. celiac disease)	6,045	8.1	1,415	5.3	866	7.9	2,708	9.1	1,056	13.8
Chemotherapy encounter	5,532	7.4	1,850	7.0	826	7.6	2,115	7.1	741	9.7
Menorrhagia	4,584	6.1	1,875	7.0	747	6.8	1,674	5.6	288	3.8
Ulcerative colitis; Crohn's disease	3,246	4.3	1,048	3.9	539	4.9	1,428	4.8	231	3.0
Peptic ulcer disease	3,175	4.2	1,131	4.3	504	4.6	1,258	4.2	282	3.7
Intestinal cancer	3,118	4.2	1,072	4.0	492	4.5	1,175	3.9	379	5.0
Uterine fibroid	3,039	4.1	1,158	4.4	534	4.9	1,154	3.9	193	2.5
Anemia, unspecified	3,021	4.0	1,402	5.3	443	4.1	1,073	3.6	103	1.3
Chemotherapy or cancer induced anemia	2,390	3.2	828	3.1	379	3.5	893	3.0	290	3.8
Stomach cancer	816	1.1	283	1.1	130	1.2	306	1.0	97	1.3
Anemia complicating pregnancy, childbirth or the puerperium	1,088	1.5	345	1.3	167	1.5	544	1.8	32	0.4
Esophageal varices	552	0.7	200	0.8	82	0.8	219	0.7	51	0.7
Endometriosis	482	0.6	180	0.7	83	0.8	189	0.6	30	0.4

Indication	All Products		Iron Dextran Users		Ferric Gluconate Users		Iron Sucrose Users		Ferumoxytol Users	
	n	% [†]	n	% [†]	n	% [†]	n	% [†]	n	% [†]
Esophageal cancer	462	0.6	144	0.5	83	0.8	174	0.6	61	0.8
Other indication (patients with none of the above diagnoses)	2,698	3.6	1,124	4.2	640	5.9	840	2.8	94	1.2
% [†] within each treatment group										

C. ANAPHYLAXIS RATES

The overall incidence rate of anaphylaxis among new users of parenteral iron was 2 per 10,000 (16 cases among 70,866 new users).(Table 13) The number of new users in this table, and all subsequent tables, is lower for both iron dextran and non-dextran iron products because for workplan two, we excluded patients aged 65 and over in one data partner because we were unable to obtain medical records to review for that population. Among 24,603 new iron dextran users there were 8 cases and among 46,263 new users of other parenteral iron products there were 8 confirmed cases. The unadjusted rates of anaphylaxis among these groups were 3 per 10,000 (95%CI 1-6 per 10,000) and 2 per 10,000 (95% CI 1-3 per 10,000) respectively.

Table 13. Total number of anaphylaxis cases confirmed by chart review and crude incidence rates

IV Iron Product	Total Number of New Users*	Total Number of Confirmed Cases	Crude Incidence Rate with 95% Exact CI
Iron dextran	24,603	8	0.03 (0.01,0.06)
Non-dextran iron products	46,263	8	0.02 (0.01,0.03)
All parenteral iron products	70,866	16	0.02 (0.01,0.04)

* Total number of new users obtained from MSDD

D. RATES OF HYPERSENSITIVITY REACTIONS

There were two patients with mild hypersensitivity reactions, ten with moderate hypersensitivity reactions, and ten with severe hypersensitivity reactions.(Table 14) All patients with anaphylaxis were also confirmed to have either moderate or severe hypersensitivity reactions. Eleven new iron dextran users had moderate or severe hypersensitivity reactions (incidence rate = 4.5 per 10,000) and nine new users of the other parenteral iron products had moderate or severe reactions (incidence rate = 2 per 10,000).

Table 14. Incidence rates of hypersensitivity (confirmed by medical record review) among new parenteral iron users

IV Iron Product	Total number of new users	Total number mild hypersensitivity reactions	Crude incidence rate of mild hypersensitivity with 95% exact CI	Total number moderate hypersensitivity reactions	Crude incidence rate of moderate hypersensitivity with 95% exact CI	Total number severe hypersensitivity reactions	Crude incidence rate of severe hypersensitivity with 95% exact CI
Iron Dextran	24,603	2	0.01 (0.00,0.03)	7	0.03 (0.01,0.06)	4	0.02 (0.00,0.04)
All Other Parenteral Iron Products (except iron dextran)	46,263	0		3	0.01 (0.00,0.02)	6	0.01 (0.00,0.03)

IV Iron Product	Total number of new users	Total number mild hypersensitivity reactions	Crude incidence rate of mild hypersensitivity with 95% exact CI	Total number moderate hypersensitivity reactions	Crude incidence rate of moderate hypersensitivity with 95% exact CI	Total number severe hypersensitivity reactions	Crude incidence rate of severe hypersensitivity with 95% exact CI
All Parenteral Iron Products	70,866	2	0.00 (0.00,0.01)	10	0.01 (0.01,0.03)	10	0.01 (0.01,0.03)

E. PREMEDICATIONS AND BRAND NAMES

Two of the seven patients (29%) with anaphylaxis who received iron dextran were treated with premedication as were four of the eight patients (50%) with anaphylaxis who received non-dextran parenteral iron products (one patient was administered an unknown type of parenteral iron). Of those who received premedication, 4 received steroids, 3 received antihistamines, and none received non-steroidal anti-inflammatory medications (Table 15). Of the seven patients who received iron dextran and developed anaphylaxis, three received INFED and for the rest the brand name was not recorded in the medical record.

Table 15. Premedication by confirmed parenteral iron administration and confirmed anaphylaxis by chart review

	All Products		Iron Dextran Users		Ferric Gluconate Users		Iron Sucrose Users		Ferumoxytol Users		Unknown Product	
	n	% [†]	n	% [†]	n	% [†]	n	% [†]	n	% [†]	n	% [†]
Confirmed Parenteral Iron Administration*	65	100.0	26	100.0	18	100.0	18	100.0	0	n/a	3	100.0
Premed: Benadryl	10	15.4	6	23.1	2	11.1	2	11.1	0	n/a	0	0.0
Premed: Steroid	8	12.3	5	19.2	2	11.1	1	5.6	0	n/a	0	0.0
Premed: Anti-inflammatory	5	7.7	3	11.5	0	0.0	2	11.1	0	n/a	0	0.0
Premed: Other	5	7.7	4	15.4	1	5.6	0	0.0	0	n/a	0	0.0
Premed: Multi	8	12.3	6	23.1	1	5.6	1	5.6	0	n/a	0	0.0
Premed: Any	18	27.7	10	38.5	4	22.2	4	22.2	0	n/a	0	0.0
Anaphylaxis Confirmed**	16	100.0	7	100.0	6	100.0	2	100.0	0	n/a	1	100.0
Premed: Benadryl	3	18.8	2	28.6	1	16.7	0	0.0	0	n/a	0	0.0
Premed: Steroid	4	25.0	1	14.3	2	33.3	1	50.0	0	n/a	0	0.0
Premed: Anti-inflammatory	0	0.0	0	0.0	0	0.0	0	0.0	0	n/a	0	0.0
Premed: Other	1	6.3	0	0.0	1	16.7	0	0.0	0	n/a	0	0.0
Premed: Multi	2	12.5	1	14.3	1	16.7	0	0.0	0	n/a	0	0.0
Premed: Any	6	37.5	2	28.6	3	50.0	1	50.0	0	n/a	0	0.0

*Of the 92 charts reviewed, 65 were confirmed to have been administered parenteral iron on the index date. Data on premedication are reported here for those 65 cases.

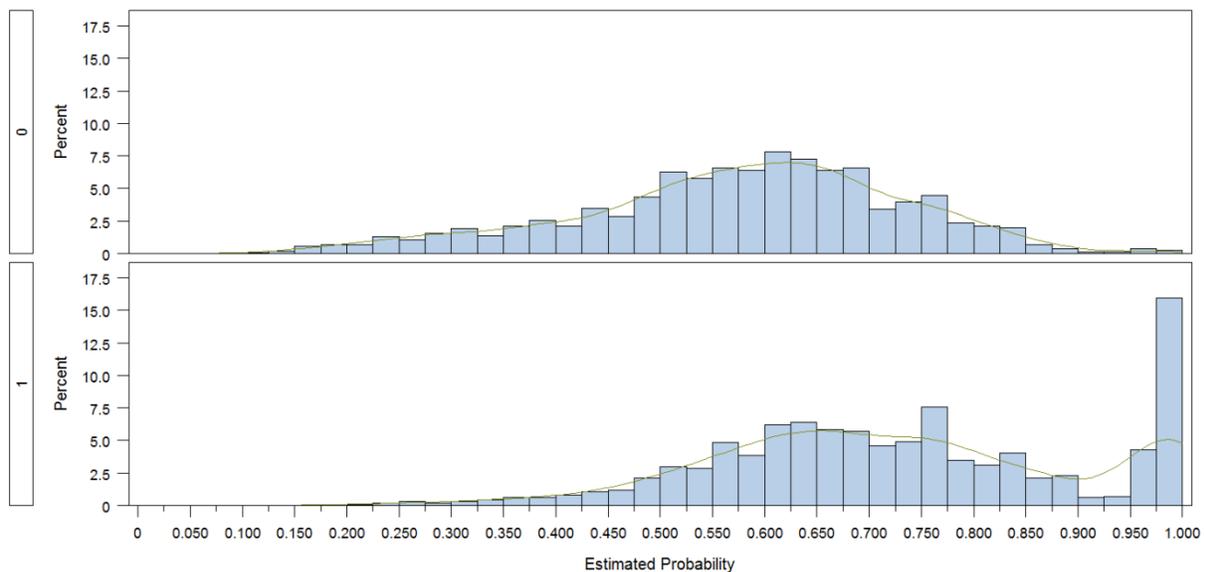
**Of the 92 charts reviewed, 16 cases were confirmed to have had an anaphylaxis episode on the index date (they all had confirmed parenteral iron administration as well). Data on premedication are reported here for those 16 cases.

F. DESCRIPTION OF CONTROLS

1. Information on propensity scores

The within-group PS distributions differ substantially across sites reflecting heterogeneity in medication prescription pattern from different Data Partners. For instance, PSs are mostly less than 0.5 at Data Partner 1 but are mostly greater than 0.5 at Data Partner 16. At some Data Partners, the PS ranges for the iron dextran users and the other iron products users differ indicating an incomplete overlap of PS distributions. For instance, as illustrated in Figure 2 below, at Data Partner 18, a large percent of iron dextran users have very high PSs close to 1 while the other iron products group has a much lower percentage of users in that range. These iron dextran users may have few comparable controls from the other group and thus making it inappropriate to include them in the comparative assessment. See Appendix 4 for histograms for all participating Data Partner sites.

Figure 2. PS histograms for Data Partner 18 by exposure group



2. Comparison of iron dextran and non-dextran parenteral iron groups for the entire population and the matched cohort

Overall, the iron dextran group had a lower proportion of patients over 65 years and more females than the comparison group; 31% of iron dextran users and 42% of non-dextrose parenteral iron users were over 65 years (standardized difference: -0.231). (Table 16) The non-dextrose parenteral iron users had a higher proportion of patients with coronary heart disease (22% vs 15% in iron dextran; standardized difference: -0.184) or hypertension (55% vs 43% in iron dextran; standardized difference: -0.229). Iron dextran was more often used in the outpatient setting than the comparison group.

Table 16. Patient characteristics by exposure group for the entire cohort before matching from MSDD

Characteristic		Iron Dextran		Other Parenteral Iron Products		Absolute Difference	Standardized Difference
		Mean / Proportion	SD / Percent	Mean / Proportion	SD / Percent		
Number of patients		24,603	100.00%	46,263	100.00%	0.000	.
Confirmed anaphylaxis cases		8	0.03%	8	0.02%	0.000	0.010
Confirmed moderate or severe hypersensitivity reactions cases		11	0.05%	9	0.02%	0.000	0.014
Age on index date	0-10 years	42	0.17%	71	0.15%	0.000	0.004
	11-19 years	307	1.25%	466	1.01%	0.002	0.023
	20-64 years	16,543	67.24%	26,109	56.44%	0.108	0.224
	65 and older	7,711	31.34%	19,617	42.40%	-0.111	-0.231
Gender	Female	19,407	78.88%	33,191	71.74%	0.071	0.166
	Male	5,196	21.12%	13,072	28.26%	-0.071	-0.166
History of:	Anaphylaxis, not related to food**	18	0.07%	37	0.08%	0.000	-0.002
	Drug allergy	652	2.65%	1,207	2.61%	0.000	0.003
	Atopic dermatitis	129	0.52%	236	0.51%	0.000	0.002
	Food, latex, insect bite allergy	52	0.21%	111	0.24%	0.000	-0.006
	Other allergy	436	1.77%	661	1.43%	0.003	0.027
	Allergic rhinitis	1,689	6.87%	2,645	5.72%	0.011	0.047
	Asthma	2,100	8.54%	3,980	8.60%	-0.001	-0.002
	COPD	2,838	11.54%	6,201	13.40%	-0.019	-0.057
	Coronary heart disease	3,593	14.60%	10,027	21.67%	-0.071	-0.184
	Hypertension	10,680	43.41%	25,348	54.79%	-0.114	-0.229
	HIV infection	71	0.29%	136	0.29%	0.000	-0.001
Current use of:	Immunosuppressive therapy	1,112	4.52%	2,732	5.91%	-0.014	-0.062
	Oral steroid use	4,275	17.38%	8,253	17.84%	-0.005	-0.012
	Injectable steroid use	4,651	18.90%	8,081	17.47%	0.014	0.037
	Antibiotic use	12,391	50.36%	22,520	48.68%	0.017	0.034
	Beta blocker use	5,212	21.18%	13,241	28.62%	-0.074	-0.173

Characteristic		Iron Dextran		Other Parenteral Iron Products		Absolute Difference	Standardized Difference
		Mean / Proportion	SD / Percent	Mean / Proportion	SD / Percent		
	ACE inhibitor	4,966	20.19%	10,297	22.26%	-0.021	-0.051
	ARB	2,317	9.42%	5,997	12.96%	-0.035	-0.113
Year of new use	2000	208	0.85%	0	0.00%	0.008	0.131
	2001	490	1.99%	19	0.04%	0.020	0.195
	2002	442	1.80%	37	0.08%	0.017	0.179
	2003	516	2.10%	137	0.30%	0.018	0.166
	2004	639	2.60%	340	0.74%	0.019	0.146
	2005	640	2.60%	509	1.10%	0.015	0.112
	2006	1,192	4.85%	1,234	2.67%	0.022	0.115
	2007	1,887	7.67%	2,392	5.17%	0.025	0.102
	2008	2,112	8.58%	5,127	11.08%	-0.025	-0.084
	2009	4,184	17.01%	7,377	15.95%	0.011	0.029
	2010	3,809	15.48%	7,934	17.15%	-0.017	-0.045
	2011	3,700	15.04%	8,488	18.35%	-0.033	-0.089
	2012	3,394	13.80%	8,944	19.33%	-0.055	-0.149
	2013	1,390	5.65%	3,725	8.05%	-0.024	-0.095
Clinical setting (where IV iron administered)	Outpatient	24,183	98.29%	42,773	92.46%	0.058	0.281
	Inpatient	290	1.18%	2,639	5.70%	-0.045	-0.250
	Emergency department	132	0.54%	853	1.84%	-0.013	-0.121

We were able to match 20,699 of the 24,603 new users of iron dextran (84%). (Table 17) Overall, this included 9 out of 16 patients with anaphylaxis. In the matched cohort, differences in the distributions of patient characteristics were not seen. (Table 17)

Table 17. Patient characteristics by exposure group: Matched cohort

Characteristic		Iron Dextran		Other Parenteral Iron Products		Absolute Difference	Standardized Difference
		Mean / Proportion	SD / Percent	Mean / Proportion	SD / Percent		
Number of patients		20,669	100.00%	20,669	100.00%	0.000	.
Confirmed anaphylaxis cases		8	0.04%	1	0.01%	0.000	0.023
Confirmed moderate or severe hypersensitivity reactions cases		11	0.05%	1	0.01%	0.000	0.028
Age on index date	0-10 years	27	0.13%	28	0.14%	0.000	-0.001
	11-19 years	194	0.94%	207	1.00%	-0.001	-0.006
	20-64 years	13,667	66.12%	13,656	66.07%	0.001	0.001
	65 and older	6,781	32.81%	6,778	32.79%	0.000	0.000
Gender	Female	16,109	77.94%	16,116	77.97%	0.000	-0.001
	Male	4,560	22.06%	4,553	22.03%	0.000	0.001
History of:	Anaphylaxis, not related to food**	16	0.08%	14	0.07%	0.000	0.004
	Drug allergy	562	2.72%	511	2.47%	0.002	0.016
	Atopic dermatitis	109	0.53%	108	0.52%	0.000	0.001
	Food, latex, insect bite allergy	41	0.20%	33	0.16%	0.000	0.009
	Other allergy	346	1.67%	316	1.53%	0.001	0.012
	Allergic rhinitis	1,404	6.79%	1,322	6.40%	0.004	0.016
	Asthma	1,714	8.29%	1,558	7.54%	0.008	0.028
	COPD	2,361	11.42%	2,267	10.97%	0.005	0.014
	Coronary heart disease	3,175	15.36%	3,153	15.26%	0.001	0.003
	Hypertension	9,313	45.06%	9,259	44.80%	0.003	0.005
	HIV infection	57	0.28%	47	0.23%	0.000	0.010
Current use of:	Immunosuppressive therapy	993	4.80%	915	4.43%	0.004	0.018
	Oral steroid use	3,590	17.37%	3,396	16.43%	0.009	0.025
	Injectable steroid use	4,025	19.47%	3,904	18.89%	0.006	0.015
	Antibiotic use	10,202	49.36%	10,127	49.00%	0.004	0.007
	Beta blocker use	4,450	21.53%	4,398	21.28%	0.003	0.006
	ACE inhibitor	4,115	19.91%	4,070	19.69%	0.002	0.005

Characteristic		Iron Dextran		Other Parenteral Iron Products		Absolute Difference	Standardized Difference
		Mean / Proportion	SD / Percent	Mean / Proportion	SD / Percent		
	ARB	2,090	10.11%	2,094	10.13%	0.000	-0.001
Year of new use	2000	0	0.00%	0	0.00%	0.000	.
	2001	15	0.07%	18	0.09%	0.000	-0.005
	2002	36	0.17%	35	0.17%	0.000	0.001
	2003	137	0.66%	137	0.66%	0.000	0.000
	2004	278	1.35%	267	1.29%	0.001	0.005
	2005	391	1.89%	399	1.93%	0.000	-0.003
	2006	865	4.19%	841	4.07%	0.001	0.006
	2007	1,516	7.34%	1,459	7.06%	0.003	0.011
	2008	1,978	9.57%	2,014	9.74%	-0.002	-0.006
	2009	4,021	19.45%	4,051	19.60%	-0.001	-0.004
	2010	3,542	17.14%	3,579	17.32%	-0.002	-0.005
	2011	3,421	16.55%	3,405	16.47%	0.001	0.002
	2012	3,167	15.32%	3,175	15.36%	0.000	-0.001
	2013	1,302	6.30%	1,289	6.24%	0.001	0.003
Clinical setting (where IV iron administered)	Outpatient	20,279	98.11%	20,289	98.16%	0.000	-0.004
	Inpatient	273	1.32%	268	1.30%	0.000	0.002
	Emergency department	119	0.58%	114	0.55%	0.000	0.003

G. ADJUSTED ODDS RATIOS FOR ANAPHYLAXIS

In the PS matching analysis, for all sites, the odds ratio of anaphylaxis for the use of iron dextran vs. other parenteral iron products, among the actual iron dextran users, was 8.001 (95% CI: 1.001-63.964; p-value 0.0499). We were unable to perform multiple logistic regression analysis due to the small number of anaphylaxis cases. In the PS stratification analysis, the odds ratio of anaphylaxis for the use of iron dextran vs. other iron products, among all parenteral iron products users was 2.74 (95% CI: 0.87-8.65; p-value 0.0859) stratified by site and PS quintile.

H. ADJUSTED ODDS RATIO FOR MODERATE TO SEVERE HYPERSENSITIVITY

In the PS matching analysis, for all sites, the odds ratio of moderate or severe hypersensitivity for the use of iron dextran vs. other parenteral iron product, among the actual iron dextran users, was 11.005 (95% CI: 1.42-85.25; p-value 0.0217). We were unable to perform multiple logistic regression analyses due to the small number of anaphylaxis cases. In the PS stratification analysis, the odds ratio of moderate or severe allergic reaction for the use of iron dextran vs. other iron products, among all parenteral iron product users was 3.099 (95% CI: 1.13-8.47; p=0.0276).

I. SENSITIVITY ANALYSES

The sensitivity analysis was overall consistent with the results of the main analysis- showing increased odds of anaphylaxis but large confidence intervals due to the small number of anaphylaxis cases (Table 18). Similarly, the sensitivity analysis for moderate or severe hypersensitivity was consistent with the main analysis. (Table 19) Due to the data refresh and privacy concerns, some patients (less than 1% of patients and none of the anaphylaxis cases) were no longer eligible and therefore removed from the original files at one data partner. None of the anaphylaxis cases were removed.

Table 18. Sensitivity analysis: Anaphylaxis

Analysis	Iron Dextran		Other Iron Products		OR	95% CI		p-value
	n	#AEs	n	#AEs				
No trimming	24,442	8	46,162	8	2.728	0.865	8.600	0.0867
Trim by 1 st and 99 th percentiles	22,422	7	42,397	4	3.075	0.806	11.723	0.1000
Trim by 2.5 th and 97.5 th percentiles	20,979	7	39,721	3	3.842	0.917	16.099	0.0656
Trim by 5 th and 95 th percentiles	19,063	7	36,118	2	4.738	0.941	23.857	0.0593

Table 19. Sensitivity analysis: Moderate or severe allergic reaction

Analysis	Iron Dextran		Other Iron Products		OR	95% CI		p-value
	n	#AEs	n	#AEs				
No trimming	24,442	11	46,162	9	3.093	1.133	8.448	0.0276
Trim by 1 st and 99 th percentiles	22,422	8	42,397	5	2.766	0.828	9.237	0.0983
Trim by 2.5 th and 97.5 th percentiles	20,979	7	39,721	4	2.908	0.789	10.713	0.1086
Trim by 5 th and 95 th percentiles	19,063	7	36,118	3	3.302	0.812	13.427	0.0952

J. PS MATCHING

Table 20 below shows no change in matching results whether or not data is stratified by data partner.

Table 20. PS matching

Outcome	Analysis	OR	95% CI	p-value
Anaphylaxis	No stratification on DP	8.026	1.004 64.164	0.0496
	Stratification on DP	8.042	1.006 64.306	0.0494
Moderate or Severe Allergic Reaction	No stratification on DP	11.040	1.425 85.516	0.0215
	Stratification on DP	11.047	1.426 85.572	0.0215

V. SUMMARY AND CONCLUSIONS

In the Mini-Sentinel population, new users of parenteral iron dextran who were not on dialysis had increased risk of anaphylaxis compared to new users of non-dextran parenteral iron products. New users of iron dextran had 8.0 times the odds (95% CI: 1.0-64.0; p-value 0.0499) of non-dextran users in matched PS analysis and 2.74 (95% CI: 0.87-8.65; p-value 0.0859) times the odds of non-dextran users in PS stratified analysis. In the Mini-Sentinel population, new users of parenteral iron dextran who were not on dialysis had 8.0 times the odds of anaphylaxis compared to new users of non-dextran parenteral iron products. While the number of anaphylaxis cases in our cohort was small, our findings are consistent with a recent publication by Wang *et al.* in Medicare patients, which reported an adjusted odds ratio of 2.6 (95%CI, 2.0-3.3; p-value < .001) for anaphylaxis among new parenteral iron dextran users compared to non-dextrose iron products. Our findings are also consistent with several smaller studies.^{16,17,23} The PPV of our overall algorithm to identify anaphylaxis was low (17%), largely due to low PPV of the criterion based upon administration of epinephrine. When excluding epinephrine from the algorithm, the PPV of the algorithm was 61.9%. This is similar to the previously PPV for this algorithm of 63.1%. Our validation results showed that restricting anaphylaxis events to those occurred on the same or next day of IV Iron exposure did not improve the performance of the algorithm and that the positive predictive value of the case definition based on an epinephrine dispensing alone on the same day as parenteral iron administration was low.

The strengths of our study include the validation of anaphylaxis cases from electronic health plan data using medical record review. In our previous study and in the previous literature, algorithms based upon electronic health plan data had PPV estimates of approximately 0.6 for identification of anaphylaxis, making medical record review necessary to avoid bias associated with identifying potential cases which are not actually anaphylaxis patients. We attempted to review all cases meeting criteria for anaphylaxis or identified with an administration of epinephrine to minimize misclassification while at the same time using a sensitive measure for more complete capture of cases. Two adjudicators independently reviewed all potential cases of anaphylaxis to reduce misclassification of the outcome. In addition, adjudicators were blinded to the specific parenteral iron product used. We also performed our study in a population of mostly younger patients- a population that not well studied before. Finally, we performed both propensity score matching and stratified analyses and used sensitivity analyses to identify the best method to report data.

Limitations of the study include the small number of confirmed anaphylaxis cases. We obtained a lower proportion of medical records than in prior Mini-Sentinel studies (88% in our prior anaphylaxis validation). In addition, for the exposure of interest, iron dextran, there was unavoidable grouping of high molecular weight and low molecular weight products, though the literature indicates that these forms are often confused and substituted in clinical practice. As a result, we were not able to estimate the risk of anaphylaxis separately for high and low molecular weight iron dextran. We did review each chart where the patient developed anaphylaxis in an attempt to ascertain whether the iron dextran agent involved was INFeD (low molecular weight) or Dexferrum (high molecular weight). Three of the eight cases of anaphylaxis in the iron dextran group did receive INFeD; for the remainder, the specific product was not documented. Finally, there was some overlap problems in PS distributions between iron dextran users and other iron products users. In consequence, we implemented trimming to the PS stratification analyses in the sensitivity analyses. PS matching is expected to account for that automatically as iron dextran users without comparable controls from the other exposure group will have no matched controls and thus excluded from subsequent regression analysis.

A. LESSONS LEARNED

1. The use of the anaphylaxis algorithm (Criteria A, B and C) after the administration of a high risk medication did not improve the PPV

Our workgroup had expected that the previously validated Mini-Sentinel anaphylaxis algorithm may have a higher PPV when used in association with a drug reported to have an increased risk of anaphylaxis. However, we found that the anaphylaxis algorithm performed similarly to the PPV we found in the previously published Mini-Sentinel anaphylaxis validation study.

2. The use of epinephrine as an indicator of anaphylaxis after administration of parenteral iron had a very low PPV

In our study, epinephrine was a poor proxy for anaphylaxis in parenteral iron users. This may be particularly poor in this group, due to the practice of ordering epinephrine routinely to the bedside when parenteral iron is ordered.

3. PS distributions differ across Data Partners reflecting substantial heterogeneity in prescription patterns

At some Data Partners, there is incomplete overlap in PS distributions between iron dextran users and other iron products users (higher propensity scores for some cases and lower propensity scores for some controls). PS matching accounts for this automatically as only iron dextran users with comparable controls will be included in subsequent analysis. Because of this heterogeneity, we lost several anaphylaxis cases in PS matched analyses that we were unable to match. For PS stratification, trimming was implemented in sensitivity analyses to remove outliers with no comparable “controls” from the other exposure group.

4. The percent of charts obtained for this study was lower than previous Mini-Sentinel projects and impacted sample size

The percent of charts we were able to obtain for this study was lower than some prior Mini-Sentinel studies. The reason for the lower availability of charts is unknown, but may depend on the differences in the participating Data Partners or providers/facilities contacted.

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VIII. APPENDICES

A. APPENDIX 1: DIAGNOSTIC AND PROCEDURE CODES FOR DIALYSIS

ICD-9-CM Diagnosis Codes									
458.21	996.56	996.68	996.73	V45.1	V56				
ICD-9-CM Procedure Codes									
39.95	54.98								
CPT-4 Procedure Codes									
36145	36800	36825	36832	90935	90945	90964	90967	90970	90999
36147	36810	36830	36833	90937	90947	90965	90968	90989	93990
36148	36815	36831	49421	90940	90963	90966	90969	90993	99512
HCPCS Procedures									
A4653	A4709	A4728	A4770	A4911	E1520	E1592	E1635	G0323	G8076
A4671	A4714	A4730	A4771	A4913	E1530	E1594	E1636	G0324	G8081
A4672	A4719	A4736	A4772	A4918	E1540	E1600	E1637	G0325	G8082
A4673	A4720	A4737	A4773	A4929	E1550	E1610	E1639	G0326	G8085
A4674	A4721	A4740	A4774	C1750	E1560	E1615	E1699	G0327	G8714
A4680	A4722	A4750	A4802	C1752	E1570	E1620	G0257	G0365	G8715
A4690	A4723	A4755	A4860	C1881	E1575	E1625	G0320	G0392	G8956
A4706	A4724	A4760	A4870	E1500	E1580	E1630	G0321	G0393	S9335
A4707	A4725	A4765	A4890	E1510	E1590	E1634	G0322	G8075	S9339
A4708	A4726	A4766							

B. APPENDIX 2: HEALTH PLAN ADMINISTRATIVE AND CLAIMS CODES USED FOR ANAPHYLACTOID REACTIONS

ICD-9-CM^a diagnosis codes:

995.0 = Other anaphylactic shock

995.2 = Other and unspecified adverse effect of drug, medicinal and biological substance (due) to correct medicinal substance properly administered;

995.3 = Allergy unspecified

999.4 = Anaphylactic shock due to serum

E930-E949 = Drugs, medicinal and biological substances causing adverse effects in therapeutic use

519.11 = Acute bronchospasm

786.1 = Stridor

458.9 = Hypotension unspecified

2009 HCPCS^b codes:

J0170 = Injection, adrenalin, epinephrine, up to 1 ml ampule

J0171 = Injection, adrenalin, epinephrine, 0.1 mg

J1200 = Injection, diphenhydramine hcl, up to 50 mg

CPT^c code:

92950 = CPR

ICD-9-CM procedure code:

99.60 = CPR

^a International Classification of Diseases, Ninth Revision, Clinical Modification

^b Healthcare Common Procedure Coding System

^c Current Procedural Terminology

C. APPENDIX 3. FINAL ALGORITHM FROM THE MINI-SENTINEL ANAPHYLAXIS VALIDATION WORKGROUP TO IDENTIFY POTENTIAL CASES OF ANAPHYLAXIS USING ICD-9-CM DATA

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

OR

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

- i. bronchospasm (519.11) or
- ii. stridor (786.1) or
- iii. hypotension (458.9) or
- iv. epinephrine (J0170 or J0171) OR
- v. injection of diphenhydramine (J1200) or
- vi. CPR (92950 or 99.60)

OR

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

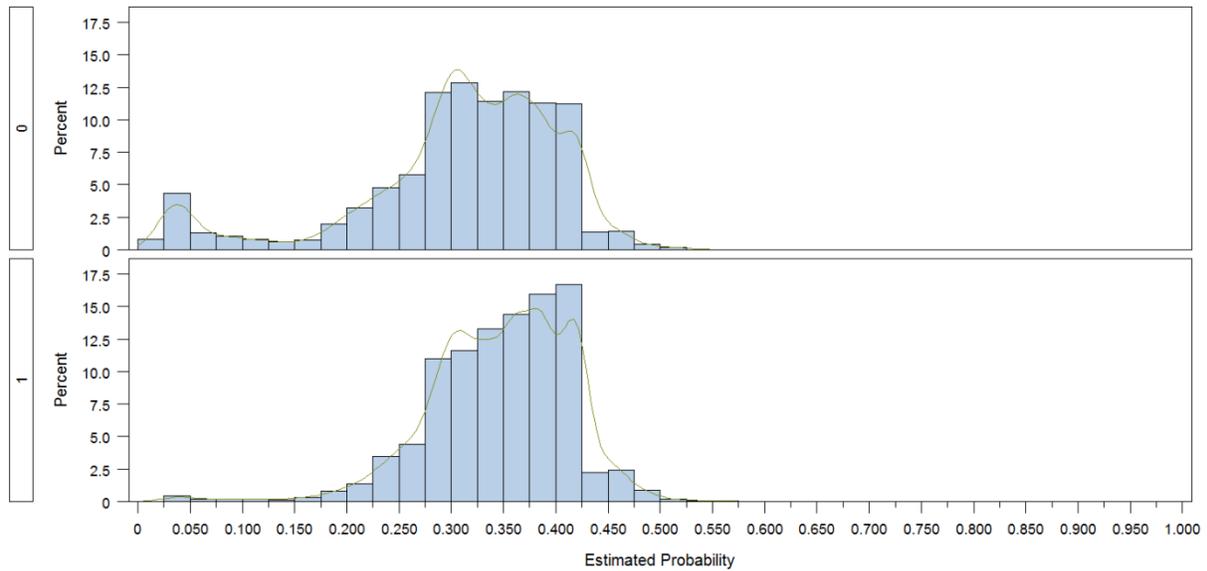
- i. **PLUS a code for one** of the following symptoms/procedures/treatments:
 1. bronchospasm (519.11) or
 2. stridor (786.1) or
 3. injection of diphenhydramine (J1200)
- ii. **and ALSO a code for one** of the following symptoms/procedures/treatments:
 1. hypotension (458.9) or
 2. epinephrine (J0170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

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

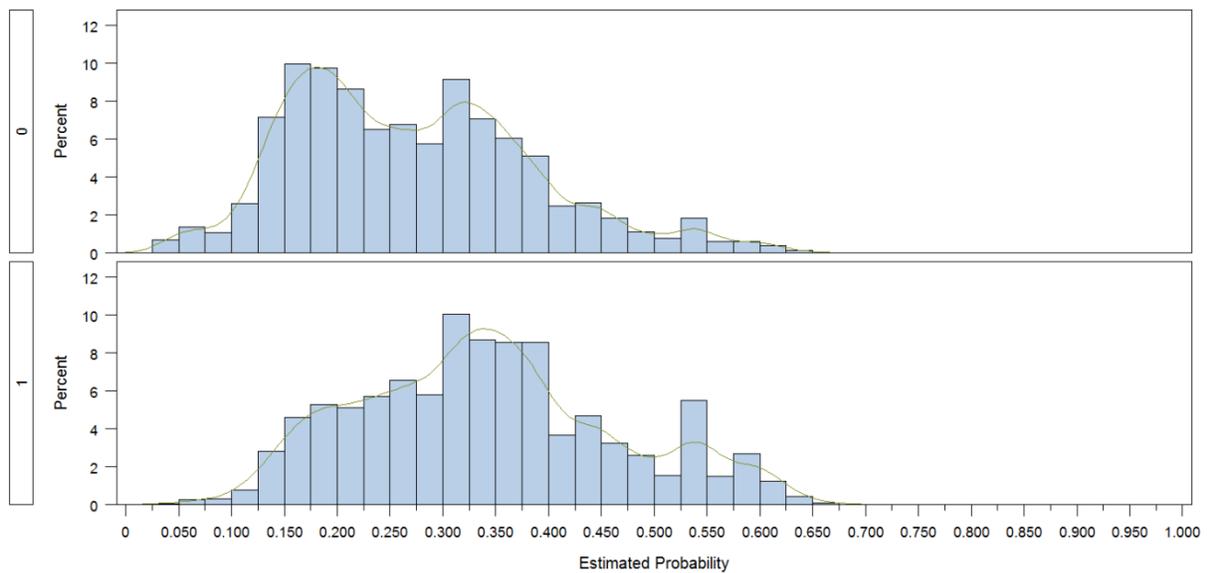
For outpatient encounters: All patients who met inclusion criteria, excluding patients with an encounter in the prior 30 days that documented an anaphylaxis code (995.0 or 999.4) were sampled.

D. APPENDIX 4. PROPENSITY SCORE HISTOGRAMS FOR ALL PARTICIPATING DATA PARTNERS

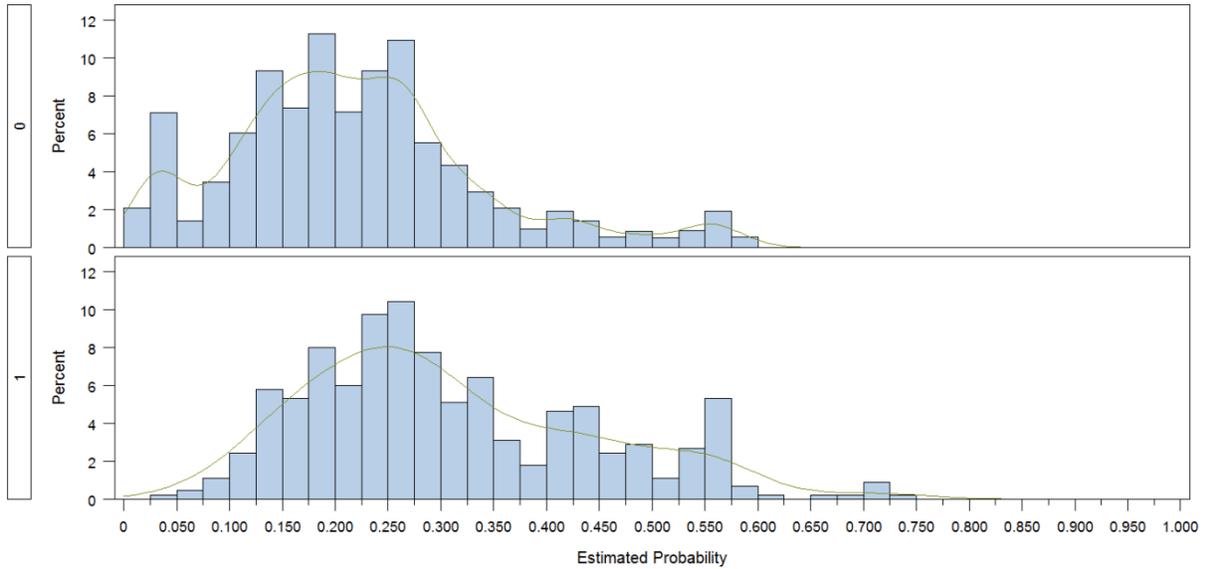
PS histograms for Data Partner 1 by exposure group



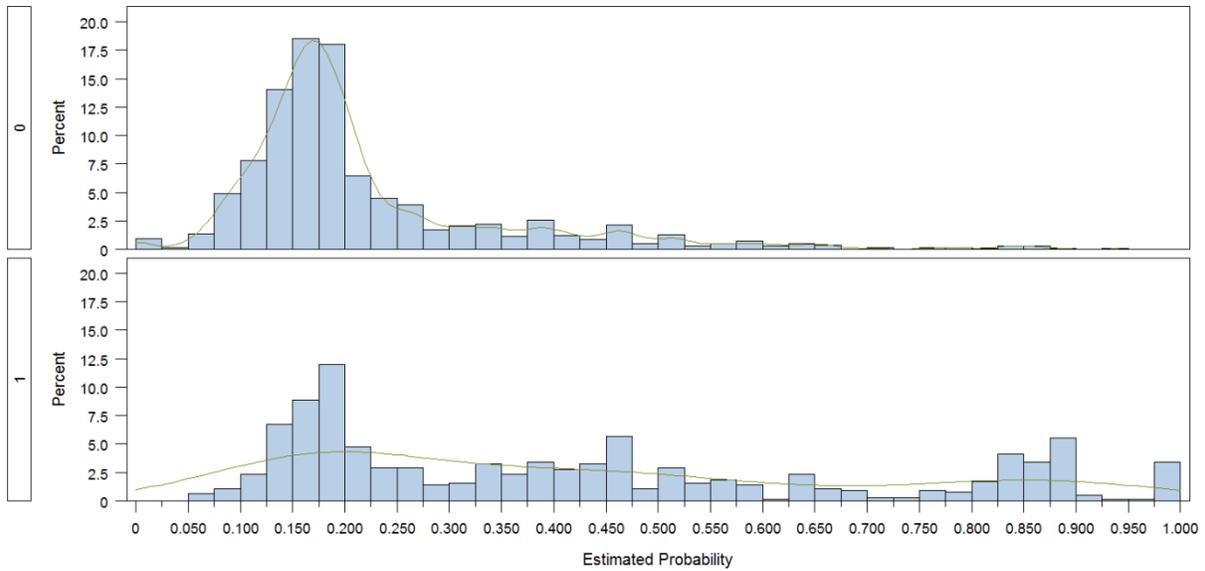
PS histograms for Data Partner 2 by exposure group



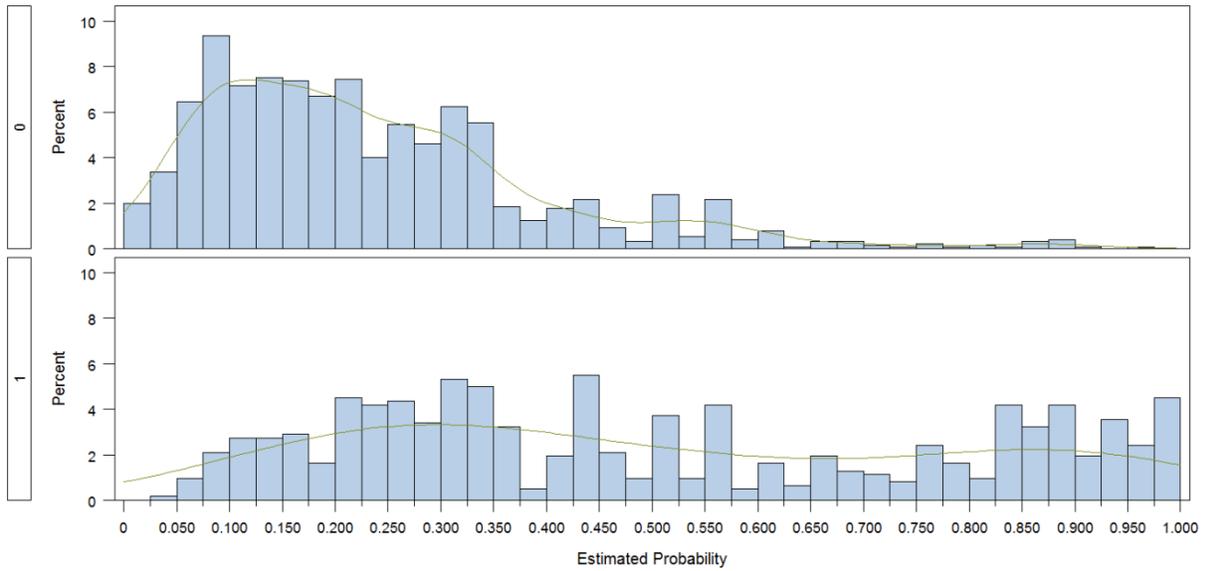
PS histograms for Data Partner 3 by exposure group



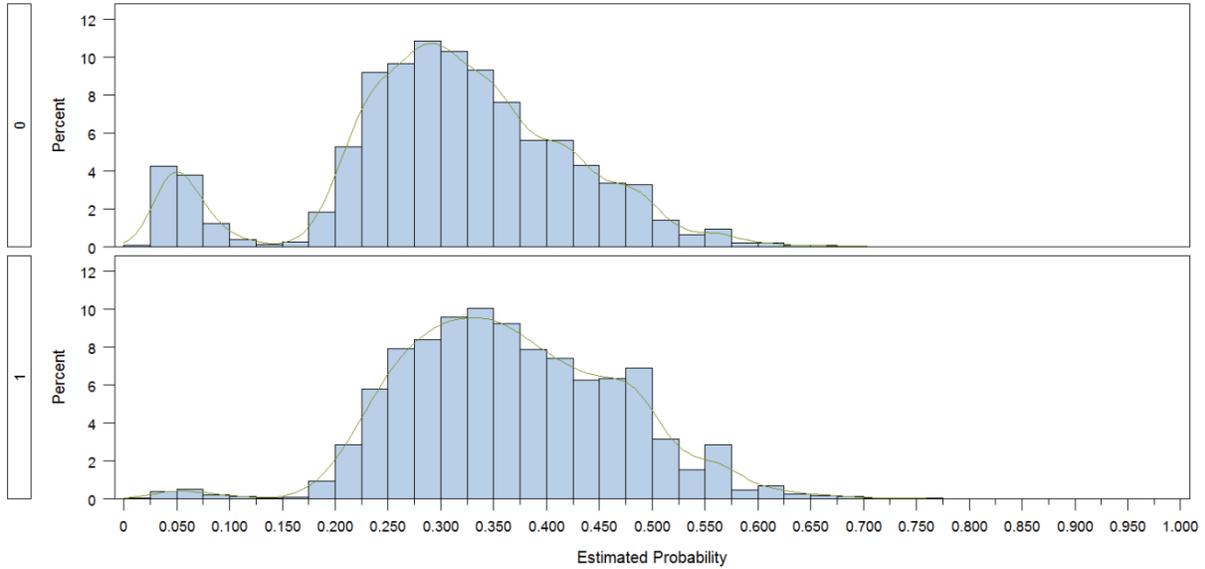
PS histograms for Data Partner 5 by exposure group



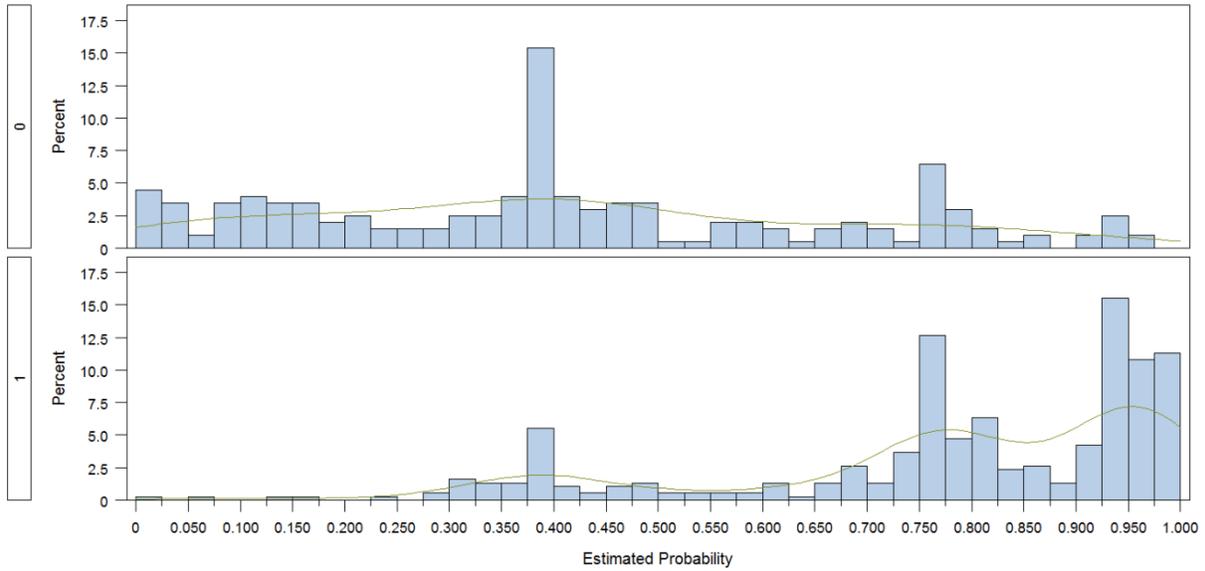
PS histograms for Data Partner 6 by exposure group



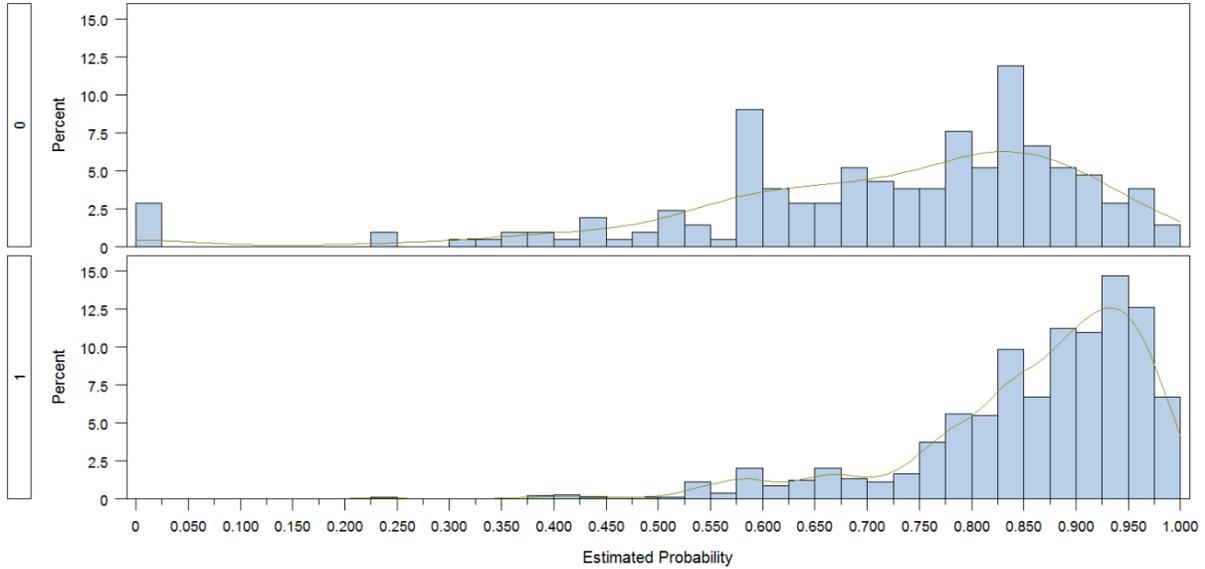
PS histograms for Data Partner 10 by exposure group



PS histograms for Data Partner 15 by exposure group



PS histograms for Data Partner 16 by exposure group



PS histograms for Data Partner 18 by exposure group

