MINI-SENTINEL ASSESSMENT PROTOCOL

PARENTERAL IRON AND ANAPHYLACTOID REACTIONS

Version 2

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Mini-Sentinel is a pilot project sponsored by the U.S. Food and Drug Administration (FDA) to inform and facilitate development of a fully operational active surveillance system, the Sentinel System, for monitoring the safety of FDA-regulated medical products. Mini-Sentinel is one piece of the Sentinel Initiative, a multi-faceted effort by the FDA to develop a national electronic system that will complement existing methods of safety surveillance. Mini-Sentinel Collaborators include Data and Academic Partners that provide access to health care data and ongoing scientific, technical, methodological, and organizational expertise. The Mini-Sentinel Coordinating Center is funded by the FDA through the Department of Health and Human Services (HHS) Contract number HHSF223200910006I.

Mini-Sentinel Assessment Protocol

Parenteral Iron and Anaphylactoid Reactions

History of Modifications			
Version	**Date**	**Modification**	**By**
V2	10/25/2013	• Additional information added to the Section I. BACKGROUND AND OBJECTIVES to include relevant literature (pages 1-3). • Additional information regarding study limitations added to Section I.F. OBJECTIVE (page 5). • Additional information regarding study limitations added to Section II., H. POTENTIAL LIMITATIONS AND ATTEMPTS TO MINIMIZE THEM, 1. Misclassification bias (pages 18-19).	Parenteral Iron and Anaphylactoid Reactions Workgroup

Mini-Sentinel Assessment Protocol

Parenteral Iron and Anaphylactoid Reactions

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I. 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."[1] Anaphylactoid reactions are immediate systemic reactions which mimic anaphylaxis but are caused by non-IgE-mediated release of mediators from mast cells and basophils.[2] They are also referred to as pseudoallergic drug reactions or non-allergic hypersensitivity reactions.[3] Notably, hypersensitivity reactions to parenteral dextran therapy have been reported since the 1960s, and are attributed to dextran-reactive IgG antibodies.[4] In general, symptoms of anaphylactoid reaction do not allow for discrimination between IgE-mediated anaphylaxis and non-IgE-mediated anaphylactoid reactions.[5] 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.[6-8] 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.[6-8] While the risk of anaphylaxis is not well-known for most medications, evaluation of spontaneous reports has led to black box warnings for a number of medications (e.g. omalizumab, aproptinin, paclitaxel), as well as withdrawal of zomepirac sodium.[9]

B. EPIDEMIOLOGY OF IRON-INDUCED ANAPHYLAXIS/ANAPHYLACTOID REACTIONS

Parenteral iron is available as iron dextran, sodium ferric gluconate, iron sucrose, and ferumoxytol (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.[10-15] Only the iron dextran products have a black 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)	J1750, J1751, J1752, J1760, J1770, J1780	Iron dextran-04/1957 INFeD-04/1974 Dexferrum-02/1996
Sodium ferric gluconate	Ferrlecit	J2915, 2916, S0098	02/1999

Generic name	Trade name	Procedure codes	FDA approval date
Iron sucrose	Venofer	J1755, J1756	11/2000
Ferumoxytol	Feraheme	Non ESRD-Q0138, ESRD dialysis-Q0139	06/2009

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.[11] 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.[12] 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.[13] 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.[16] 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.[17]

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.[10] 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.[18]

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.[19] 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.[20]

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).[14] 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.[15] 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.[21] 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.[22]

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.[23]

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.[24] 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.[25]

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.[6,7,26] These studies are summarized in the *Mini-Sentinel Systematic Evaluation of Health Outcome of Interest Definitions for Studies Using Administrative Data: Anaphylaxis Report*.[27] In this report there were two studies which evaluated the validity of health plan administrative data to identify anaphylaxis[6,26] and an additional study was published after the search results for the Mini-Sentinel report were completed.[7]

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.[6] 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 ambulatory 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.[26] 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.[7] Administrative and claims data from hospitalizations, emergency department visits, and ambulatory encounters were assessed. Medical record review was conducted and cases were confirmed based upon the *Summary Report of the Second National Institute of Allergy and Infectious Disease/Food Allergy and Anaphylaxis Network symposium*.[1] 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).[28] 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. The workgroup report recommended chart review validation when using the algorithm in future medical product safety assessments, due to the low PPV.

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 vs. low molecular weight iron dextran in claims data given the fact that both have the same name and the same billing code.[29] Low molecular weight iron and the other iron products had lower rates of anaphylaxis according to the authors than high molecular weight iron.

E. SUMMARY OF BACKGROUND

In summary, the epidemiology of parenteral iron-induced anaphylactoid or anaphylactic reactions is not well-described. Evidence from a large comparative safety study of the risk of anaphylaxis between various IV Iron products is lacking. 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 proposal is to perform a one-time assessment of the association between parenteral iron products and anaphylactoid/anaphylaxis reactions. The FDA and workgroup recognize the potential limitations of the study, such as the limited ability to differentiate between high and low molecular weight iron products (described in detail in Section I), but believe the study will still produce useful information about the association in a large, diverse, population-based cohort. The results from this assessment are *not* expected to provide definitive evidence of a causal relation. They will be interpreted in the larger context of all that is known about the association from various sources, such as randomized controlled trials and post-market reports.

II. STUDY DESIGN AND METHODS

A. DATA SOURCE

This assessment will include all Mini-Sentinel Data Partners who can provide data to the analysis.

B. IDENTIFICATION OF NEW-USERS OF DRUGS OF INTEREST

We propose to use a "new-user" cohort design.[30] We will identify health plan members with a first administration of a parenteral iron preparation during the period January 1, 2000 to June 30, 2013. We note that not all Data Partners will have data for the entire study period. Use of parenteral iron preparations will be identified using the procedure codes shown in Table 1. We will not identify parenteral iron administration using the National Drug Codes (NDCs), because in a summary table analysis we found the use of IV iron products identified as by NDCs in the Mini-Sentinel Distributed Database to be quite low (~3,000 vs. ~200,000 identified by procedure codes, see Section H). Given that anaphylaxis is a rare event, we decided that this number is too low to identify an adequate number of events among users.

We refer to the procedure date of the first administration of the iron preparation as the *index date*. We will require 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 (ambulatory) visits, or inpatient visits; and (3) no procedure codes for dialysis (Appendix 1). Dialysis patients were excluded from analysis because they represent less than half of the population receiving parenteral iron in the MSDD, their prescribing patterns appear 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 will be ignored because they usually represent administrative gaps rather than actual disenrollment.

The exposure group will be new users of iron dextran. The comparison group will be new users of other parenteral iron products. We will identify use of iron preparations in the inpatient, emergency department, and outpatient settings, although we expect the majority of parenteral iron use to be in the outpatient setting. For patients who may be eligible for more than one new use episode during the study period, only their first eligible episode will be included in the analysis.

C. IDENTIFICATION OF OUTCOME OF INTEREST

We will employ the algorithm developed by the Mini-Sentinel Anaphylaxis Validation Workgroup to identify potential cases of anaphylaxis using health plan data (Appendices 2 and 3).[28] We will identify cases of potential anaphylaxis occurring on the day of or the day after exposure to parenteral iron. Because we expect that the number of cases identified will be small, we will further include a more sensitive algorithm that will identify patients who received epinephrine the same day or the day after being administered parenteral iron. We will review these epinephrine cases using the same methods as anaphylaxis cases. Chart abstractors and adjudicators will be blinded to whether cases were identified using the anaphylaxis algorithm or from epinephrine administration.

D. CHART REVIEW VALIDATION OF CASES OF POTENTIAL ANAPHYLAXIS

The chart review will follow an approach modified from the previous Mini-Sentinel validation studies, 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 algorithm for anaphylaxis (Table 2); (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.

We will obtain all relevant portions of the medical record. The record will be redacted, abstracted, and reviewed. Because the number of anaphylaxis cases will likely be small, the goal is to validate all potential cases. Two physicians will review abstracted information and, if they feel it necessary, redacted charts and make judgments about whether anaphylaxis occurred. They will use the clinical definition developed by a recent consensus group and published by Sampson *et al.* as the gold standard for determining whether anaphylaxis occurred.[1] Only events classified as cases of anaphylaxis, determined based on the clinician definition developed by Sampson *et al*. will be in the primary analysis (Table 2).

Table 2. Clinical criteria for diagnosing anaphylaxis for use in primary analysis[1]

Anaphylaxis is highly likely when any of the following 3 criteria are fulfilled:
1. Acute onset of an illness (minutes to several hours) with involvement of the skin, mucosal tissue, or both (e.g., generalized hives, pruritus or flushing, swollen lips-tongue-uvula) AND AT LEAST ONE OF THE FOLLOWING: 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)
2. Two or more of the following that occur rapidly after exposure to a likely allergen for that patient (minutes to several hours): a. Involvement of the skin-mucosal tissue (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)
3. Reduced blood pressure after exposure to known allergen for that patient (minutes to several hours): 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

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

For secondary analyses, clinician adjudicators will divide all potential case as (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 3).[31] We will use moderate and severe allergic reactions as a separate outcome variable in secondary analysis.

Table 3. Grading system for generalized hypersensitivity reactions for use in secondary analysis[31]

Grade	Defined by
1 – Mild (skin and subcutaneous tissues only)*	Generalized erythema, uticaria, periorbital edema, or angioedema
2 – Moderate (features suggesting respiratory, cardiovascular, or gastrointestinal involvement)	Dyspnea, stridor, wheeze, nausea, vomiting, dizziness, or abdominal pain
3 – Severe (hypozia, hypotension, or neurologic compromise)	Cyanosis or $SpO_2 \leq 92\%$ at any stage, hypotension (systolic blood pressure < 90 mm Hg in adults), confusion, collapse, loss of consciousness, or incontinence
*Mild reactions can be further subclassified into those with and without angioedema (see text).	

E. IDENTIFICATION OF COVARIATES

Table 4 lists the covariates the workgroup will obtain from the 183-day period preceding (and including) the index date. Age on index date and gender will be identified from the MSDD's demographic files. Diagnostic codes recorded during inpatient, outpatient, or emergency department encounters will be obtained from the MSDD's diagnosis file.

Table 4. 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
HIV infection	Yes/No	V08, 042
Chronic obstructive pulmonary disease (COPD)	Yes/No	491, 492, 496
Coronary heart disease	Yes/No	413, 414
Primary hypertension	Yes/No	401
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

Confounder	Categorization	Identified by ICD-9-CM code(s) (unless otherwise noted)
		immunomodulators (abatacept, adalumumab, anakinra, canakinumab, certolizumab, dimethyl fumarate, etanercept, fingolimod, golimumab, infliximab, lenalidomide, mitoxantrone, natalizumab, pomalidomide, rilonacept, teriflunomide, thalidomide, tocilizumab, and ustenkinumab), 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 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	n/a

Confounder	Categorization	Identified by ICD-9-CM code(s) (unless otherwise noted)
	department	

*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.

†Define use as a dispensing (fill) in the outpatient pharmacy dispensing file for 183 days preceding and including the index date

F. FOLLOW-UP

Follow up will begin on the index date, and end on the first occurrence of anaphylaxis or one day after the index date, whichever occurs first.

G. ANALYSIS

1. **Sites with zero outcome events or use of only one iron product**
   Because anaphylaxis is a rare outcome, and because we had several sites in the feasibility analysis with zero anaphylaxis events, we expect there will be several sites in the actual assessment with zero anaphylaxis events. We will exclude Data Partner sites that have no outcome events, after medical record review, from the inferential analysis described in section G5. Because our final outcome is a risk ratio rather than a risk difference and because all analyses will stratify on site, Data Partner sites with zero outcome events will contribute no data to the relative risk analysis. We believe the bias introduced by combing 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 will be excluded from the inferential analysis. However, when calculating the absolute incidence, we will perform our analysis without and without sites with zero outcome events or use of only one iron product (See section G3 below).

2. **Comparison of baseline characteristics**
   We will compare the baseline characteristics between new users of iron dextran and new users of other iron products, overall and at each Data Partner (Table 5). We will use 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]

Table 5. Baseline characteristics

	Iron dextran N (%)	Other parenteral iron products N (%)
Age on index date 0-4 years 5-18 years 19-44 years 45-64 years 65 and older		
Gender Female Male		
History of anaphylaxis, not related to food		
Drug allergy		
Atopic dermatitis		
Food, latex, insect bite allergy		
Other allergy		
Allergic rhinitis		
Asthma		
HIV infection		
COPD		

	Iron dextran N (%)	Other parenteral iron products N (%)
Coronary heart disease		
Hypertension		
Immunosuppressive therapy		
Oral steroid use		
Injectable steroid use		
Antibiotic use		
Beta blocker use		
ACE inhibitor use		
ARB use		
Year of new use 2000 2001 2002 2003 2004 2005 2006 2007 2008 2009 2010 2011 2012		

	Iron dextran N (%)	Other parenteral iron products N (%)
2013		
Clinical setting where IV iron is administered* Outpatient Inpatient Emergency department		

* Use on the index date; for patients receiving IV iron in more than one clinical setting on the index date, report use in each setting for which it is documented

3. **Calculation of incidence**
   We will calculate the incidence of anaphylaxis for new users of iron dextran and new users of other parenteral iron, with 95% CIs. We will calculate the overall incidence with and without sites with users but no anaphylaxis events and site with users of only one parenteral iron product, as well as incidence by Data Partner.

4. **Indications of use**
   We will identify 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 will allow patients to have more than one potential indication. For those patients receiving parenteral iron who do not have any of these diagnostic codes, we will categorize as "other indication". For patients categorized as "other indication", we will obtain a list of all diagnostic codes within 7 days prior to the index date. Diagnostic codes for patients with "other indication" will be 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 malabsorbtion, 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

Diagnosis	Identified by ICD-9-CM code(s)
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
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

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

a. Estimation of relative risk

We will employ two propensity score-based approaches – matching[32] and stratification[33] – to investigate the association between the use of iron dextran and anaphylaxis, with use of other parenteral iron products as the comparison group. We will assess the covariate balance after matching and stratification. The propensity score is defined as the probability of receiving iron dextran given the measured confounders. We use the propensity score methods as our primary approach because the number of anaphylaxis events is expected to be small and the number of confounders is relatively large. The propensity score approach overcomes this issue by allowing us to adjust for all measured confounders simultaneously through a composite summary score.[33] We will estimate 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.

Propensity score matching will be conducted within sites. We will match one iron dextran user with one other iron product user using 1:1 nearest-neighbor matching without replacement

with a caliper of 0.05.[34] Unmatched patients will be excluded from subsequent analyses. Each Data Partner will transfer an aggregated dataset of the matched cohort, which includes only the number of users and outcome events in each treatment group, to the project team. The project team will then estimate the odds ratio of the confirmed anaphylactoid/anaphylaxis event, from the Sampson criteria, comparing iron dextran users with other iron product users. The aggregated dataset will only include 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 estimate the average treatment effect among the treated (ATT). Thus, we will also do propensity score stratification to estimate the population-wide average treatment effect (ATE).

In propensity score stratification, each Data Partner will divide 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 will transfer an aggregated dataset consisting of the within-stratum numbers users and anaphylaxis events in each treatment group. If sample size allows, the project team will fit a 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. If the number of anaphylaxis events is too small to stratify on both site and the within-site PS strata, we will consider stratifying on PS strata only or collapsing certain sites with few anaphylaxis events. 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).

6. Secondary analyses.

a. Multivariable-adjusted outcome logistic regression analysis

Within the larger Data Partners sites, we will apply an outcome logistic regression analysis adjusting for the same confounders and compare the results with those from the propensity score approach.[34] If the results from propensity score analysis and regression analysis at large Data Partner sites differ, we will reassess our data and propensity score model to ensure accuracy of the data and model. If necessary, we will perform a sensitivity analysis for unmeasured confounding by calculating the Rosenbaum bounds for propensity score matched data.[35]

b. Moderate and severe hypersensitivity reactions

Moderate and severe hypersensitivity reactions, adjudicated using methods in Brown's study, will be combined as a single outcome variable in a secondary analysis.[31] We will then analyze the risk of a moderate or severe hypersensitivity reaction among iron dextran users compared to other parenteral iron users, as described above.

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

Table 7. Sample size power calculations

Baseline risk per 10000 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%

Baseline risk per 10000 patients	Relative Risk	Power
9.50	1.70	81.1%

H. POTENTIAL LIMITATIONS AND ATTEMPTS TO MINIMIZE THEM

1. Misclassification bias

Bias could be introduced by the misclassification of the exposure, parenteral iron, or the outcome, anaphylaxis. We will 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. We will have two adjudicators independently review all potential cases of anaphylaxis to reduce misclassification of the outcome. This will reduce potential false positives but will not address false negatives. Adjudicators will be blinded to the specific parenteral iron product used. For the exposure of interest, iron dextran, we expect there will be some unavoidable grouping of high molecular weight and low molecular weight forms. However, since the literature indicates that these forms are often confused and substituted in clinical practice, it seems necessary to combine them in our study. As a result, we will not be able to estimate the risk of anaphylaxis separately for high and low molecular weight iron dextran. We will review each chart where the patient developed anaphylaxis in an attempt to ascertain whether the iron dextran agent involved was INFeD or Dexferrum. In addition, for all cases of anaphylaxis we will collect information about whether the patient received premedication (e.g., diphenhydramine, IV fluids, or corticosteroids) and, if so, which medications were used.

2. Confounding

Confounding could be introduced if iron dextran and other iron products are prescribed for different reasons that are also predictive of the outcome of interest. It is possible that some providers may avoid iron dextran in patients they believe to be at high risk for anaphylaxis or in general, due to the perceived risk of anaphylaxis. We have identified a list of potential confounders that will be adjusted for in the analysis. The fact that anaphylaxis is a rare outcome does make traditional adjustment for confounding, such as multivariable-adjusted outcome regression analysis, difficult. Thus, we will also employ propensity score analysis to adjust for confounding.

There was an interest in performing a stratified analysis of the association between parenteral iron use and anaphylaxis by indication. However, because the feasibility analysis indicates that the number of patients with anaphylaxis will be low, we anticipate that it is unlikely we will have adequate power to perform these stratified analyses. In this case, indication will be used to describe the population of study.

3. Generalizability

This study is drawn from a database of privately and publically insured populations. As such, it may not be generalizable to other populations. Similarly, dialysis patients were not included,

due to different prescribing patterns among dialysis and potentially different clinical symptoms. Thus, the results of this study may not be generalizable to patients on dialysis.

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IV. 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.