MINI-SENTINEL ASSESSMENT PROTOCOL

THROMBOEMBOLIC EVENTS AFTER IMMUNOGLOBULIN ADMINISTRATION

Version 3.0

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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.

History of Modifications

Version	Date	Modification	By
V3	04/23/2014 – 6/19/2015	• Revised *Objectives (B. Secondary Objectives)* and *Methods (A. Data Source and Study Population, B. Study Design and Analysis Plan, and D. Identification of Outcome of Interest)* to reflect changes in exposure and outcome definitions for the arterial and venous thromboembolic event endpoints in the primary self-controlled analyses. • Updated *Limitations* to address the limitations of restricting venous thromboembolic events to outpatient treatment of immunoglobulin. • Elaborated on exploratory analyses in *Methods* (*G.2 Exploratory cohort analyses* and *H.2 Exploratory cohort analyses)*. Revised inclusion and exclusion criteria related to immunoglobulin users. Described potential for exposure and endpoint definitions to be revised based on chart validation results. • Modified *Methods (H.2 Exploratory cohort analyses, 3. Disease risk score)* and *Appendix A* to regroup immunoglobulin indications based on considerations of therapeutic mechanism, dose administered, baseline thromboembolic event risk and parsimony. • Revised description of disease risk score estimation (*H.3. disease risk score, Appendix A, and Appendix D* to reflect updated method of calculation, including population in which disease risk score coefficients were estimated. • Modified chart validation criteria to incorporate physician documentation of diagnoses. Added diagnosis criteria to Table 4, 5. • Updated Table A 1 to reflect revised categories of conditions for immunoglobulin use. Added designation of	Thromboembolic events after immunoglobulin administration workgroup

Version	Date	Modification	By
		"recognized" indications and footnotes to explain the abbreviations for code type and dose. • Updated tables in *Appendix D* to address changes in covariate definitions and modified categorizations and codes used for risk factors. Added footnote to Table D 2 to define code type abbreviations. • Updated References. • Made many less substantive changes in the interests of completeness, accuracy, and flow.	
V2	09/20/2013 – 4/22/2014	• Added authors to the title page. • Updated *Background* to clarify immunoglobulin exposure definition and administration history. • Revised secondary objectives to include a formerly 'exploratory objective'. • Updated enrollment requirement to accommodate for potential truncation of control window. • Modified Table 3 to reflect updated objectives. • Added Figures 1 and 2 with their respective detailed explanations to describe Identification of Ig New Users. • Revised *Methods (D. Identification of outcomes of interest)* to reflect changes in the chart ranking and chart validation processes. • Revised *Methods (E. Potential Confounders)* to clarify how the disease risk score will be applied in analyses. • Added *Limitations* to address limitations of exploratory analyses, code and outcome selection, and brand identification. • Added Figures 3, 4, 5 & 6 to describe proposed statistical analysis and further illustrate the self-controlled risk interval design. • Provided more details on the exploratory analyses. • Elaborated on disease risk score calculation.	Thromboembolic events after immunoglobulin administration workgroup

Version	Date	Modification	By
		• Included more details about requirements for thromboembolic event validation. • Modified Table 4 language. • Included statistical test used for power calculation. • Updated Appendix A to address the challenges in confirming the route of Ig administration and indication being treated for each case. • Included rationale for adopting high dose and low dose Ig definition in Appendix A. • Added additional indications and codes to Table A 1 based on further review: Rubella PEP, Varicella PEP, Hepatitis A PEP, Measles PEP, Allogeneic bone marrow transplantation. • Revised Appendix C to reflect updated chart review process. • Added codes for diabetes and chronic renal disease to Table D3. • Clarified use of codes identifying pregnancy in Appendix D. These codes will only be applied during chart confirmation. • Updated References. • Made many less substantive changes in the interests of completeness, accuracy, and flow.	

Mini-Sentinel Assessment Protocol
Thromboembolic Events after Immunoglobulin Administration

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I. BACKGROUND

The Blood Safety Continuous Active Surveillance Network (Blood-SCAN) is a Task Order under the Mini-Sentinel pilot that aims to develop a claims-based active surveillance system for FDA-regulated blood components and blood-derived products. As part of the Blood-SCAN activities, the purpose of this Workgroup is to conduct a retrospective protocol-based assessment of thromboembolic events (TEE) after non-specific immunoglobulin (Ig) administration and validate the algorithms used to identify the exposure and the outcome. The FDA-approved non-specific Ig products are listed in Table 1. There are 12 different products. Hyperimmune globulin products were excluded from this study, since this group of products have very specific indications and are used by a relatively small population of patients. The majority of Ig use is via the intravenous route (IV), though some products are available for intramuscular (IM) or subcutaneous (SC) administration. Formulations and manufacturing processes vary across products so it is important to distinguish among them.

Table 1. Immunoglobulin Products with FDA Approval

Product Name	Route	Approval Date	Product Description
Bivigam	IV	December 19, 2012	Liquid 10%
Carimune NF, Panglobulin, Sandoglobulin	IV	June 7, 1984	Lyophilized powder for reconstitution
Flebogamma; Flebogamma DIF	IV	December 15, 2003 July 27, 2010	Liquid 5% Liquid 10%
Gammagard S/D; Gammagard S/D Less IgA	IV	February 18, 1986	Lyophilized powder for reconstitution
Gammagard Liquid	IV or SC	April 27, 2005 (SC approved July 11, 2011)	Liquid 10%
GamaSTAN S/D	IM	January 11, 1944	2 mL and 10 mL vials
Hizentra	SC	March 4, 2010	Liquid 20%
Octagam	IV	May 21, 2004	Liquid 5%
Gamunex; Gamunex-C	IV or SC	August 27, 2003 (SC approved October 13, 2010)	Liquid 10%
Privigen	IV	July 26, 2007	Liquid 10%
Gammaplex	IV	September 17, 2009	Liquid 5%
Gammaked (Identical to Gamunex)	IV or SC	August 27, 2003	Liquid 10%

Ig is a purified plasma fraction of polyclonal immunoglobulin G, and production of Ig products involves pooling human plasma from thousands of donors.[1] Ig is used to treat a wide variety of conditions, including primary and secondary immune deficiencies, autoimmune disorders, and inflammatory disorders (See Appendix A). While indication varies by product, many of the diagnoses in Appendix A are considered "off-label" for all the Ig products. Doses used vary by indication, with low dose Ig for immune deficiencies and high doses to suppress inflammatory or immune-mediated processes.[2] Doses can be classified as high dose (≥ one gram/kg administered over ≤ five days) and low dose defined as any dose less than high dose. Depending on the indication for Ig, some patients will have only 1 treatment

episode while others will have repeated episodes. A treatment episode typically consists of Ig administered on as few as one and as many as five consecutive days. In chronic users treatment will recur every three to four weeks. Some users will have only sporadic repeated treatment episodes.

A case series describing the possible association of TEE with IVIg was first reported in the medical literature in 1986, and in 2002 the FDA began requiring manufacturers to include a warning about TEEs in IVIg product packaging.[3,4] By 2007, at least 55 cases of IVIg-linked TEEs had been described in publications,[5] and investigators' estimates of the frequency of TEEs among patients receiving IVIg range from one to 13%.[6,7-12] In 2010, an increase in TEEs reported following Octagam administration resulted in a voluntary recall in both the US and the EU.[13,14] Subsequent investigation by FDA and Octapharma, the manufacturer of Octagam, discovered increased coagulation Factor XIa in implicated lots.[15] Increased Factor XIa was also found in lots from other Ig products by investigators at FDA.[16] Researchers at the Paul Ehrlich Institute (PEI) tested 19 lots from five different manufacturers and identified both kallikrein and FXIa as major contaminants in IVIgs.[17] In response to this issue, manufacturers of Ig products "instituted validated risk mitigation strategies to address the risk of FXIa in immune globulin products and to address the risk of harmful procoagulant activity in these products."[15,16,18-20] FDA convened a public workshop May 17-18, 2011 to address procoagulant activity in Ig products. Prior to and after this workshop the agency conducted testing for procoagulant activity. In addition, it reviewed adverse event data from multiple sources including the FDA Adverse Event Reporting System (FAERS), European passive reporting databases, and a large healthcare claims database, the HealthCore Integrated Research Database (HIRD, a MS Data Partner). Although these reports are subject to limitations, they provided a clearer picture of the nature and frequency of these events after Ig administration. In June 2013 FDA announced that it would require manufacturers to add information on thrombosis to the current boxed warning in the labels of all IV human immune globulin products and to add a boxed warning to the labels of all SC and IM human immune globulin products to highlight the risk of thrombosis and to add information on its mitigation.[21]

Several proposed pathophysiological mechanisms provide biologic plausibility for an association between Ig use and TEEs. As discussed above some Ig products have been found to contain activated coagulation factors.[17,22] In addition, Ig can increase blood viscosity beyond the normal upper limit of 1.9 centipoise (cp),[23] perhaps by triggering erythrocyte aggregation and platelet activation.[6,24] Even small changes in serum viscosity may affect capillary blood flow. Thus, a slight viscosity increase such as that caused by Ig, although not higher than one cp, may be sufficient to precipitate a thromboembolic episode in a predisposed individual.[23] Finally, a reversible increase in arterial vascular tone has also been reported to occur following IVIg infusion.[25,26]

The literature provides some indication about the likely window of elevated risk for TEEs after Ig exposure. Ig has been implicated in both arterial and venous TEEs, and the time of onset has been observed to differ for the two types of TEE. The time of onset of thrombosis relative to IVIg administration was reported in a literature review that yielded 63 cases (51 arterial, 12 venous).[27] Forty-one percent occurred within four hours of the infusion, and 63% occurred within 24 hours. Only eight percent were reported more than one week after the IVIg infusion. In the review, 77% of arterial events occurred in the first 24 hours after the infusion, whereas 46% of venous events occurred within 24 hours. In a review of a larger series of case reports,[10] arterial thrombosis accounted for 66% of the 92 cases, of which nearly two-thirds were strokes and one quarter were acute myocardial infarctions (AMI). Deep vein thrombosis (DVT) or pulmonary embolism (PE) accounted for 24 of the 31 venous

thromboembolic events with the remainder accounted for by superficial vein thrombosis (three events), central retinal vein occlusion (3), and transverse sinus vein thrombosis (1).

FDA recently assembled a case series of reports received in the FAERS between January 1, 2006 and December 31, 2010.[28] There were 209 unique TEEs reported. The average age was 54.1 years (median 58.6; range 82 days to 88 years). Arterial events accounted for 58% (n = 122), venous for 36% (n = 76), 2.9% (n = 6) of patients had both, and 2.4% (n = 5) were classified as type unspecified. Stroke and AMI accounted for the large majority of patients with arterial events (73% of 128 patients); DVT and PE accounted for the large majority of patients with venous events (74% of 82 patients). Five patients with arterial events (3.9%) had multiple-site events and this was the case for ten patients with venous events (12.2%). For cases in which time of onset was known, arterial events occurred most commonly during infusion or in the first 24 hours after infusion (61.4%). In contrast, venous events occurred most commonly two or more days after infusion (74.6%), with 52.5% occurring more than five days after the infusion. The most common risk factors present among people with arterial events were male gender, hypertension, hyperlipidemia, and coronary disease. The most common risk factors among those with venous events were use of oral contraceptives, previous DVT, or in-dwelling catheter.

Estimates of TEE frequency from published case reports, case series, and the FAERS have well-known limitations. Case series reports tend to be small and are often gathered from patients with a single common diagnosis or a single institution. Data from FAERS are subject to under reporting and incomplete information, and lack a denominator. Only one large cohort study has examined the association between Ig and TEE.[29] This study compared the effects of different Ig products on same day or next day TEE in a large administrative claims database with no medical record confirmation of exposures or events. In that analysis, of 11,785 people exposed to Ig products, 122 (one percent) had a TEE on the same day as an Ig administration, and TEE incidences per 1,000 exposed people ranged from 6.1 to 20.5 across the different products.

This Blood Safety Continuous Active Surveillance Network (Blood-SCAN) protocol-based assessment will provide the first large scale examination of the risk of TEE following IVIg with medical record confirmation. The Mini-Sentinel Distributed Database used by Blood-SCAN allows FDA to examine health outcomes after medical product use in over 178 million people. The assessment will bring greater clarity to previous estimates of the frequency of TEE after Ig, and it will benefit from pharmacoepidemiologic methods which enable calculation of the observed risk of TEE attributable to product use. In addition, the assessment may identify particular patient risk factors that could further inform risk mitigation efforts.

Information from modular programs has informed the design of this protocol based assessment. Early modular program results identified 185 TEE among 32,112 unique IVIg users within 14 days of Ig use during 2006-2012. After updating the exposure and outcome code lists, subsequent modular program feasibility analyses identified approximately 55,000 IVIg infusions, 3000 SCIg infusions, and 8000 IMIg injections during 2006-2012. In the 27 days following these treatment episodes, 347, 11, and 16 TEEs were observed in the IV, SC, and IM treatment groups, respectively. Given the relative paucity of exposure to IM and SC Ig, this study will focus on IVIg. Table 2 summarizes these data among IVIg products. Across the event types (arterial and venous), event rates were substantially higher during days 0-2 compared to days 3-27.

Table 2. Summary of Incident IVIg Use and TEE in the MSDD between January 1, 2006 and December 31, 2012, by Ig Product, Exposure Extension Period* and Type of TEE Event

	New Users	New Episodes	Days at Risk	New Events	Events/100K Days at Risk	Events/Person-Year at Risk
Brand-Identified IVIg						
Arterial TEE						
0-2-day exposure ext	18,689	36,594	123,432	49	39.70	0.145
3-27-day exposure ext	18,689	36,594	840,496	64	7.61	0.028
Venous TEE						
0-2-day exposure ext	18,499	36,018	121,639	37	30.42	0.111
3-27-day exposure ext	18,499	36,018	827,612	84	10.15	0.037
Brand Unknown IVIg						
Arterial TEE						
0-2-day exposure ext	10,482	18,823	63,252	29	45.85	0.167
3-27-day exposure ext	10,482	18,823	436,551	26	5.96	0.022
Venous TEE						
0-2-day exposure ext	10,387	18,606	62,582	27	43.14	0.157
3-27-day exposure ext	10,387	18,606	431,463	31	7.18	0.026

*For some indications Ig may be re-administered within a 27 day period. This is especially true for SC products which are often administered weekly for chronic use. These nuances were not accommodated in the modular program results presented here but our proposed exposure criteria (Appendix B) account for this.

II. OBJECTIVES

This Mini-Sentinel safety assessment seeks to address the question: What is the effect of immunoglobulin (Ig) treatment on the risk of thromboembolic events (TEE)? There are several aspects of the relationship that are of interest to the FDA. These include: the relative and absolute magnitudes of TEE risk attributable to Ig; the temporal relationship between Ig exposure and the two TEE types (arterial and venous); and whether risk of arterial or venous TEE differs by Ig dose, product/brand, indication for use, the patient's baseline TEE risk/risk factors, and the patient's past exposure to Ig. Because IVIg is more commonly used than SCIg or IMIg, and most TEE adverse events reports have concerned IVIg, the primary exposure of interest is IVIg.

A. PRIMARY OBJECTIVES

1. With the use of a self-controlled risk interval design, estimate the relative risk of chart-confirmed arterial TEE (stroke or AMI), comparing the risk vs. control intervals following Ig administration among new users of any IVIg.
2. With the use of a self-controlled risk interval design, estimate the relative risk of chart-confirmed venous TEE (DVT or PE), comparing the risk vs. control intervals following outpatient Ig administration among new users of any IVIg.

B. SECONDARY OBJECTIVES

1. For each primary objective, explore whether the relative risk is modified by
    a. Product/brand
    b. Dose

c. Type of indication (primary immunodeficiency, secondary immunodeficiency, inflammatory/other)

2. With the use of a self-controlled risk interval design, estimate the relative risk of the composite outcome of any TEE (arterial or venous), comparing the risk vs. control intervals following Ig administration among new users of any IVIg (inpatient or outpatient administration for arterial TEE; outpatient administration for venous TEE).
3. Quantify the positive predictive value of the arterial, venous, and composite TEE definitions.

C. EXPLORATORY OBJECTIVES BASED ON CHART CONFIRMED DATA

1. For each primary objective, explore whether the relative risk is modified by
   a. History of the outcome event (i.e. arterial or venous TEE)
   b. Baseline TEE risk (assessed using disease risk scores)
   c. Treatment episode number
   d. Days since treatment
   e. Infusion rate (may be incomplete or unobtainable)
   d. Recency of product: whether Ig product was delivered (and presumably manufactured) in 2011/2012 after efforts were undertaken to reduce risk of TEE.

D. EXPLORATORY OBJECTIVES BASED ON ADMINISTRATIVE DATA

1. Describe the overall trajectory of TEE incidence (without medical record confirmation), among all eligible Ig-exposed individuals, for any route of administration, by time after Ig exposure and re-exposure, to evaluate the choice of the risk and control window and examine differences by route of administration, comparing risk after receiving Ig by IM or SC versus risk after IVIg.
2. Describe the overall trajectory of TEE incidence, (without medical record confirmation), among all eligible individuals with indications for Ig, including those untreated by Ig, to provide an additional comparative framework that may be helpful in assessing what TEE risk would have been among the Ig-treated individuals had they never been treated with Ig.
3. Estimate the attributable risk – the number of TEEs per 1000 new-users of IVIG and per 1000 episodes of IVIG treatment. (Please note this objective will use both chart confirmed (TEE cases) and non-confirmed (number of users) data).

III. METHODS

A. DATA SOURCE AND STUDY POPULATION

This assessment will include all Data Partners contributing data to the Mini-Sentinel Distributed Database (MSDD) that (a) participate in chart retrieval and (b) have patients meeting the preliminary eligibility criteria for the primary self-controlled analyses. The population will consist of individuals of any age who were members of any of the participating Data Partners during the period of interest (January 1, 2006 through December 31, 2012). Within this period, individuals will be included in the primary analysis if they (a) were new users (defined below) of any IVIg product during the study period, (b) had a chart-confirmed arterial TEE within days 0-2[i] or 14-27 or a chart-confirmed venous TEE within

[i] Because Ig treatment may be administered on multiple consecutive days, every day on which Ig is received is considered a day 0, other days that are one day after Ig treatment are called day 1, other days that are two days

days 0-27 following an IVIg infusion, (c) maintained health plan enrollment from the date of IVIg treatment initiation through the TEE date. The requirement of at least 183 days of enrollment prior to IVIg initiation was selected to optimize the ability to identify history of any Ig use, prior TEE and other disease risk factors while balancing the possibility of a large loss of case numbers with a stricter enrollment criterion. Individuals will be included in exploratory cohort analyses of TEE incidence during all available follow-up time post-Ig exposure if they had a recognized indication for Ig use (defined in Appendix A) and were new users of any Ig product (IV, SC or IM) during the study period (exploratory objective D.1). Individuals will be included in exploratory cohort analyses of TEE incidence among all individuals possibly eligible for Ig treatment (exploratory objective D.2); comparing individuals who received Ig with those who did not) if they had an indication for Ig.

Thus, our primary analyses will be restricted to new-users of IVIg during pre-defined risk intervals and comparison intervals. One set of exploratory analyses will examine risk during all available post-Ig follow-up in new users. Another set of exploratory analyses will include individuals with Ig indications (non-users and initiators of Ig treatment).

B. STUDY DESIGN AND ANALYSIS PLAN

To address the primary and secondary objectives we will employ a self-controlled design to compare the risk of TEE between a pre-specified post-treatment risk interval and control interval. We use the term "self-controlled" for this method because instead of comparing outcomes across individuals who received different treatments (or no treatment), we are comparing outcomes across different time periods within the same treated individuals. We will compare risk during the post-treatment period of concern versus risk during a comparison time interval that is sufficiently remote from treatment to be assumed to have returned to baseline risk. Exploratory analyses will evaluate the choice of the risk and control window. A number of the risk factors for TEE -- that would be difficult to control for in a cohort analysis comparing individuals who received Ig versus alternatives (or no treatment) -- will not be problematic for this self-controlled analysis because they can be assumed to be stable within a person between the risk and control interval. The workgroup considered possible comparison groups suitable for a cohort design and will perform some cohort analyses to address the "exploratory" objectives, but for our primary analyses these were deemed too vulnerable to confounding.

In the self-controlled analysis, the risk interval will be day 0-2, i.e., the day(s) of Ig exposure plus the two days after Ig exposure, for arterial TEE, and day 0-13 days for venous TEE. Days 14-27 after exposure will be the control window for both the arterial and venous outcomes. For the venous TEE endpoint, the self-controlled analyses will include only risk-or-control-window events that occurred following outpatient infusions of IVIg.. Among patients who are hospitalized, the risk of venous TEE may increase

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after Ig are day 2, etc. The risk interval will include days 0-2 for arterial outcomes and days 0-13 for venous outcomes. Thus, if Ig is administered over 3 consecutive days the "0-2" risk interval for arterial outcomes would be 5 days in duration. To account for minor interruptions in a multiple-day treatment episode, (e.g., due to weekends) we will allow a gap of one or two days. For example, if Ig is administered on Friday, Monday and Tuesday, the "0-2" risk window would be seven days in duration, and would include three day 0s, two day 1s (Sat and Wed) and two day 2s (Sun and Thurs). A control period will begin 14 days after the most recent Ig exposure. Thus, if Ig was last received on a Tuesday, the control period will begin on a Tuesday two weeks later. To avoid bias that would arise if a TEE on an initial day 0 cancelled a planned 2nd day of Ig treatment, we will ascertain by chart review and use the number of days of treatment planned (if available).

substantially with prolonged immobility,[30] which would violate our study design's assumption that for a given patient, the risk of a TEE is constant across the designated risk and control windows.

The choice of these windows was based on what is known about the temporal relationship between Ig use and arterial and venous TEE incidence from prior literature and FAERS data.[27,28] Risk and control windows will be defined relative to the proximate IVIg date, viz., the date of the IVIg treatment that occurred on or prior and proximal to the TEE date. To ensure that patients had observable risk and control periods, we will require that each patient had health plan enrollment and no IVIg use for at least 20 days following the proximate IVIg date, with 7 observable days being the minimum length for the control period. (A caveat: if a patient was deceased upon discharge from a risk-window TEE hospital encounter, that patient would still be included in the analysis.)

The primary and secondary self-controlled analyses will use chart-confirmed data and will be carried out as soon as chart-confirmed data are available. For each TEE confirmed to have occurred in the risk or control interval, we will assess whether or not it occurred in the risk interval. This binary outcome will be examined in relation to the odds of being in the risk interval (rather than the control interval) that would be expected under the null hypothesis, that Ig is not associated with an increased risk of TEE. Because our concern is focused on safety rather than effectiveness, we specify a one-side null hypothesis that the relative risk of TEE on a day during the defined risk interval directly after immunoglobulin exposure compared with a day in the unexposed control interval is not greater than 1.0.

The plan is shown schematically in Table 3 below. The exposure risk interval and control interval have been specified a priori and therefore the charts for exposed cases will be sampled from these windows. Change in TEE risk in relation to time-since-Ig-treatment will be further explored in the analyses using automated data. These exploratory analyses will evaluate, but not inform, the choice of the risk and control intervals.

Since currently there is no universally accepted test for procoagulant activity, we will conduct an exploratory analysis in which we will stratify the episodes of Ig treatment on calendar year of administration and compare relative risk estimates from the more recent time period (2011-12) with those from 2006-2010. The more recent time period should encompass the period when some manufacturers modified their processes to decrease procoagulant activity. However, even among brand identified IVIg, we will not necessarily be able to differentiate whether or not a patient received product produced under the processes intended to reduce residual procoagulant activity.

Table 3. Overview of Analysis Methods

Ig Exposure	TEE Outcome	Analysis	Method	Notes
Any IVIg	Arterial TEE	Primary	Self-controlled risk interval using chart-confirmed data	Risk interval: 0-2 days Control interval: 14-27 days
Any IVIg administered in an outpatient setting	Venous TEE	Primary	Self-controlled risk interval using chart-confirmed data	Risk interval: 0-13 days Control interval: 14-27 days
Subgroups defined by IVIg product, dose, and indication	Arterial TEE	Secondary	Self-controlled risk interval using chart-	Risk interval: 0-2 days Control interval: 14-27

Ig Exposure	TEE Outcome	Analysis	Method	Notes
			confirmed data, subgroup analysis	days Also, days since treatment (day 0 versus the control period, day 1 versus the control period, and day 2 versus the control period)
Subgroups defined by IVIg product, dose, and indication	Venous TEE	Secondary	Self-controlled risk interval using chart-confirmed data, subgroup analysis	Risk interval: 0-13 days Control interval: 14-27 days Also, days since treatment (day 0 versus the control period, day 1 versus the control period, and day 2 versus the control period)
Arterial TEE endpoint: Any IVIg administration in an inpatient or outpatient setting Venous TEE endpoint: Any IVIg administration in an outpatient setting	Any TEE (venous or arterial)	Secondary	Self-controlled risk interval using chart-confirmed data	Risk interval: 0-2 days (arterial); 0-13 days (venous) Control interval: 14-27 days
Subgroups defined by history of outcome event, baseline arterial TEE risk, days since treatment, treatment episode number, infusion rate, and calendar year of treatment (especially 2006-2010 versus 2011-2012 to assess the possibility that newer manufacturer processes are producing safer Ig products)	Arterial TEE	Exploratory	Self-controlled risk interval using chart-confirmed data, subgroup analysis	Risk interval: 0-2 days Control interval: 14-27 days Also, days since treatment (day 0 versus the control period, day 1 versus the control period, and day 2 versus the control period).
Subgroups defined by history of outcome event, baseline venous TEE risk, days since treatment, treatment episode number, infusion rate, and calendar year of treatment (especially 2006-2010 versus 2011-2012 to assess the possibility that newer manufacturer processes are producing safer Ig products)	Venous TEE	Exploratory	Self-controlled risk interval using chart-confirmed data, subgroup analysis	Risk interval: 0-13 days Control interval: 14-27 days Also, days since treatment (day 0 versus the control period, day 1 versus the control period, and day 2 versus the control period)
Any route of Ig (IV, SC, IM)	Arterial	Exploratory	Cohort analysis using	Explore varying risk

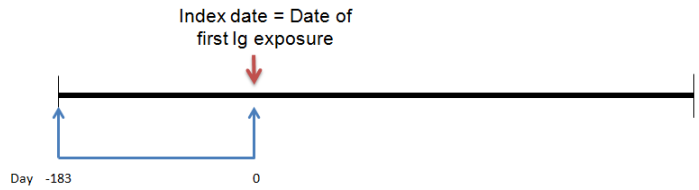
Ig Exposure	TEE Outcome	Analysis	Method	Notes
	TEE, Venous TEE		electronic data using all eligible Ig-exposed individuals (IV, IM, or SC), without chart confirmation	intervals: Arterial – 0-1, 2-7, 8-30, 31-90, 91-180, 181-365, Venous – 0-1, 2-7, 8-30, 31-90, 91-180, 181-365 Explore heterogeneity of risk between subgroups, e.g., IV vs SC, IM users.
Any route of Ig (IV, SC, IM)	Arterial TEE, Venous TEE	Exploratory	Cohort analysis using electronic data using individuals with Ig indication with and without Ig treatment, without chart confirmation	Explore calendar time trends. Explore TEE incidence among exposed vs. unexposed individuals

C. IDENTIFICATION OF IMMUNOGLOBULIN NEW USERS

We will identify health plan members of any age with administration of any Ig product (IV, SC, or IM) using CPT, HCPCS and ICD-9-CM procedure codes and National Drug Codes (NDC) for non-specific Ig (Appendix B). We will restrict our primary and secondary analyses to "new-users" of Ig products with a currently active license.[31] We will refer to the encounter date, admission date, or dispensing date for the first Ig exposure 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 (see Figure 1): 1) continuous health plan enrollment with pharmacy and medical benefit and 2) no use of any Ig product. We will exclude individuals who initiated more than one product of interest on the index date. Gaps of 45 days or less in enrollment, pharmacy or medical benefit will be ignored because they usually represent administrative gaps rather than actual disenrollment.

Figure 1. New Ig User Definition

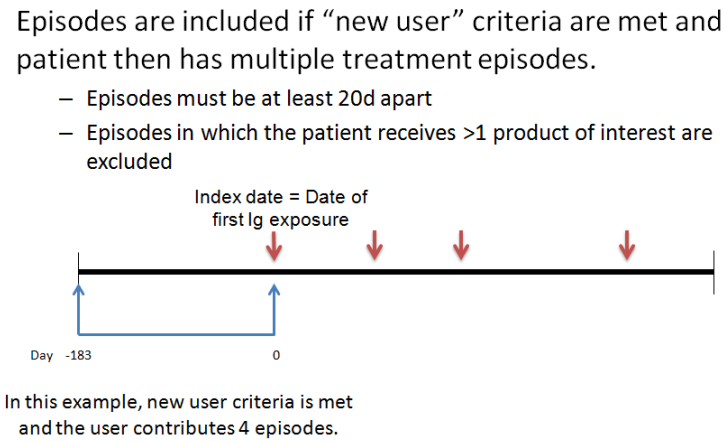
- Continuous plan enrollment for ≥ 183 days before the index date
- No administration of any Ig product for ≥ 183 days before the index date



New user must have at least 183 days of enrollment and no Ig use

Although the primary and secondary analyses are restricted to "new-users", we are not restricting follow-up to the first episode of IVIg treatment; follow-up of the new-users will also include any subsequent IVIg treatment episodes (until there is an outcome event during a risk interval or control interval, see Figure 2). The rationale for restricting to new users is not because we are primarily interested in the first exposure to IVIg, but instead to ensure that important information is known about each treatment episode examined – including (a) whether it is a 1st, 2nd 3rd etc. episode of treatment, (b) that relevant covariates can be ascertained during the 183-day baseline period, and (c) that our sample does not over-represent "survivors" (who have survived an unknown number of earlier IVIg treatments without a TEE).

Figure 2. User Contributing Multiple Episodes



The primary analysis will be focused on risk of TEE after Ig in all IV products combined. As previously described, several secondary and exploratory stratified analyses will be conducted, with subgroups defined by Ig product, Ig dose, history of TEE, Ig treatment episode number and Ig indication. Data on characteristics used to stratify patients in these analyses will be obtained through available administrative data and (where possible) confirmed during chart review. For example, product will be captured by medical record review, product-specific HCPCS codes, and product-specific NDC codes. We will report the source of the product-specific information (medical record vs. HCPCS vs. NDC codes). For exploratory analyses that rely only on electronic administrative data available in the MSDD, where information on Ig dose administered is typically missing, we will infer dose based on based on what is typical for a given Ig indication, and we will classify Ig dose as high, low, or unclassifiable (see Appendix A).

D. IDENTIFICATION OF OUTCOMES OF INTEREST

The primary outcomes of interest are arterial TEE (ischemic stroke and AMI) and venous TEE (DVT and PE) identified by an ICD-9-CM code (Appendix C).

Ig recipients are believed to be at an increased risk for thrombosis in both the arterial and venous circulation due to high blood viscosity or infusion of plasma constituents that raise the risk of clotting. The risk window is slightly different for arterial and venous events, although the period of greatest risk for both seems to fall within one week of infusion. Arterial events are concentrated during the first 24 hours and venous events are observed most typically two or more days after infusion.[27] Primary

analyses will examine arterial and venous events separately due to different risk windows and different risk factors. The secondary outcome of interest is the composite outcome of any TEE (arterial or venous). All TEE diagnoses on or after the index date will be captured for exploratory analysis of the risk and control windows, however only TEE on days 0-27 (0-2 and 14-27 for arterial TEE) after an Ig dose will be included in the self-controlled risk interval analysis. To restrict to incident cases and avoid classifying follow-up visits as events, the primary analyses will only use the first confirmed arterial TEE (or venous TEE for analyses of venous outcomes) during the 4 weeks post treatment. In other words, only the first diagnosis of an arterial or venous TEE during days 0-27 after Ig use will be considered an outcome event, and any subsequent episodes of Ig treatment and subsequent outcome diagnosis codes will not be included in primary analyses.

A well-validated algorithm for all TEE is not available, though an AMI algorithm has been validated in Mini-Sentinel.[32] The Mini-Sentinel Protocol Core has reviewed and recommended algorithms for stroke, PE and DVT. A Mini-Sentinel systematic review of cerebrovascular accidents documents algorithms with high positive predictive values.[33] The literature is not as extensive for venous TEE. The venous TEE codes included are based on the Mini-Sentinel Protocol Core recommended algorithm, which has been well-validated in hospital claims. The key source of information about this algorithm is a review of 3456 cases hospitalized between 2005 and 2007 in a large number of hospitals.[34] The PPV for any acute venous thrombosis for a venous TEE code in a secondary position was 75%. To capture the serious event of cerebral venous thrombosis, two codes (325.xx and 437.6) were added to the Mini-Sentinel algorithm but the PPV for these is based on limited data.[35] The 453.8 code series was removed from the algorithm because it refers to upper extremity thrombosis, which may be related to a central venous catheter rather than a pro-thrombotic effect of the infused Ig.

For the ascertainment of potential venous TEEs following outpatient administrations of IVIg, we will include primary or unspecified position diagnosis codes from inpatient hospitalizations. In assessing arterial TEE risk, where we will consider IVIg administrations which occur in both inpatient and outpatient settings, all inpatient arterial TEE diagnoses (any position) will be selected for chart review. The choice of a broader endpoint definition for the arterial TEE endpoint is due to the fact that under standard coding practices, events that develop during the course of a hospital stay would be listed as secondary diagnoses on hospital discharge and billing forms.[36]

All TEE algorithms for use in the assessment will be subjected to validation in the validation protocol. Definite cases (see section J) will be considered in the primary analyses. Outcomes were selected primarily based on likelihood that they could be validated using objective criteria. Transient ischemic attacks (TIA) and non-MI coronary syndromes (e.g. unstable angina, ICD-9-CM code 411) were considered but excluded due to subjective validation criteria. Also excluded were a number of less common types of thrombosis, particularly those that are likely related to comorbidities (e.g. portal vein thrombosis is typically related to severe liver disease). Outcomes less specific to thrombosis, such as abdominal ischemia, were excluded. Hemorrhagic stroke was considered because it can be a consequence of cerebral venous occlusion, but ultimately excluded because most hemorrhagic strokes are not related to a cerebral venous occlusion. Most of these outcomes are severe enough that medical attention should be sought if they occur. However, there may be a lag between onset and diagnosis for venous TEE, particularly DVT.

E. POTENTIAL CONFOUNDERS

Because the primary study design is self-controlled, the analysis will be inherently adjusted for measured and unmeasured confounders that do not vary over relatively short periods of time, such as age, gender, race/ethnicity and chronic disorders (though the severity of some of these might wax or wane).

A time-varying covariate that is of interest is the potential reduced risk of TEE due to Ig anti-inflammatory effects. This would imply that the total effect of Ig treatment on TEE risk may include a longer term benefit mediated by an anti-inflammatory causal pathway as well as a harm due to short-term risk of thrombosis. An anti-inflammatory benefit might tend to bias upwards our estimate of the short term relative risk of TEE after Ig, if the beneficial pathway reduces risk during our designated control interval 3-4 weeks post-treatment. Exploratory analyses of the trajectory of TEE incidence over time since last dose will help evaluate the possibility of time-varying confounding by anti-inflammatory effects of Ig. Another time-varying covariate is pregnancy which may increase the risk of TEE. A treatment episode will be excluded if the individual is pregnant or post-partum, based on chart review, during either the risk or control interval for that treatment episode, as this impacts TEE risk and pregnancy-related TEE codes are not included in the outcome definition.

The exploratory analyses are not self-controlled; they will be cohort analyses implemented by Cox regression (described in more detail below in section H). They will adjust for measured TEE risk factors that might be confounders in between-person comparisons, using a disease risk score summarizing the relation of TEE risk to the demographics, healthcare utilization, type of indication for Ig use (as categorized in Appendix A), comorbidities and treatments identified during the 183-day baseline period. Appendix D lists the variables that will be used to measure TEE risk factors during the baseline period preceding the index date. The purpose of combining the TEE risk factors into a summary disease risk score is two-fold, 1) to stratify self-controlled analyses by level of risk in order to evaluate possible effect modification whereby IVIg may be more or less safe according to level of TEE risk, and 2) to adjust for potential confounders in the exploratory cohort analyses that will compare exposed individuals versus unexposed individuals. Age on the index date and sex will be determined from the MSDD's demographic file. Calendar year will also be included in disease risk score calculations to account for any changes in practice that may influence event risk or detection. As in the primary self-controlled analyses, pregnant and post-partum women will be excluded from the exploratory cohort analyses. Codes used to define periods of pregnancy for the cohort analyses are listed in Appendix D.

Conditions listed in Appendix D will be identified by ICD-9-CM diagnosis codes recorded during an outpatient, inpatient, or emergency department visit from the MSDD's diagnosis file. Prescription drugs listed in Appendix D will be ascertained from MSDD's outpatient pharmacy dispensing file using NDCs. Over-the-counter use (e.g. aspirin) will not be captured unless prescribed and billed to insurance. Due to the sparseness of race data across Data Partners, race will not be collected. Appendix A provides codes to determine Ig indication from electronic data for use in exploratory analyses of all Ig users and to select a cohort of Ig users and non-users who all have an indication for Ig use.

In addition to stratification by quantile of disease risk score, history of TEE is of particular interest as an effect modifier because this is readily evaluable clinically and is already used to guide TEE prevention recommendations for Ig use. Secondary analyses of each primary outcome (arterial, venous) will assess whether history of that outcome event (arterial, venous) may be an effect modifier of the association.

Similarly, type of indication (Appendix A), dose, product, treatment episode number, and time since last dose are important clinically relevant factors that may modify the association.

F. LIMITATIONS

As noted above, the primary and secondary analyses employ a self-controlled design, so only confounding which varies over short periods will affect our results. Since the potentially anti-inflammatory effect of TEE may vary over our selected risk and control intervals, days 0-2 after IVIg may be riskier than days 14-27 not only due to an elevation of risk during days 0-2 but also due to a reduction in risk during days 14-27 because inflammation has been reduced. The exploratory cohort analyses will be used to help assess the plausibility of these possible competing explanations: if risk during days 14-27 is found –in the cohort analyses – to be similar to risk during periods even more remote from Ig exposure, and similar to risk in people with no Ig exposure, then we would be more confident in inferring that risk was elevated on days 0-2. On the other hand, if the exploratory cohort analysis finds that risk on days 0-2 is similar to risk in never-treated individuals (who have similar indications and similar levels of the disease risk score) then we might infer that a relative risk found in the self-controlled analysis is attributable to a beneficial anti-inflammatory effect.

Also, since pregnancy is a time varying factor, pregnant patients will be excluded. We understand that confounding will be present in the Cohort Analyses. Thus, these analyses are designated as exploratory and FDA does not intend to take regulation action based on the information obtained in these analyses.

Another limitation to the study is that we are investigating only 4 TEE outcomes: MI, stroke, DVT, and PE. Other TEE outcomes were excluded due to potential confounding (upper extremity DVT and central lines) or due to the difficulty in developing objective diagnostic criteria (TIA, non-MI coronary syndromes).

In assessing the risk of venous TEE following IVIg treatment, we restricted to outpatient IVIg treatments to reduce the risk of time-varying confounding by hospitalization and immobility. While this decision helps to ensure the interval validity of the study, it will limit the external validity of our findings. For the venous TEE endpoint, our study sample may have better overall health status and a lower baseline risk of venous TEE compared to patients receiving IVIg in inpatient settings.

Limitations related to coding, such as the lack of a well validated venous algorithm, will be addressed through the chart confirmation process.

Additional potential limitations are related to the chart confirmation process itself. In order to confirm exposures and outcomes, a patient chart must be available and contain sufficiently specific information to meet our pre-specified outcome criteria. In a prior Mini-Sentinel study, 22% of the charts were not available for review and additional charts lacked brand-specific information.[37] In our study, brand identification may be a challenge because non-brand specific codes exist and the location of the brand of Ig administered to the patient could be recorded in a variety of places. In an informal survey of several workgroup members' institutions, this information was located in the medication administration record, the nurse's notes, or in the pharmacy (but not in the patient chart). For some of the exploratory objectives (such as history of TEE, baseline risk of TEE, treatment episode number, and infusion rate), the ability to draw meaningful conclusions will rely on the quality and quantity of information recorded

by healthcare providers. If the necessary data elements simply were not recorded, we will not be able to gather this information and the data may be insufficient to analyze.

G. FOLLOW-UP

1. Self-controlled analyses

For our primary analyses we will include new-users of IVIg who had a chart-confirmed TEE during a post-treatment risk interval or control interval. In analyses of arterial TEE, we will include only the first arterial TEE during the four weeks following a treatment episode; in analyses of venous TEE, we will include only the first venous TEE during the four weeks following a treatment episode. Ordinarily, a patient's control window will be 2 weeks in length (days 14-27 following the proximate Ig date). Several factors may result in truncation of the patient's control window: end of the study period, disenrollment not attributable to death, another episode of Ig treatment, or a pattern of frequent Ig administration. If any of these events takes place during days 21-27 following the proximate Ig date, the control window will be shortened and this will be accounted for in the analysis. However, if a patient has fewer than 7 observable control period days, the patient will be excluded as uninformative unless the shorter observable period is due to death.

2. Exploratory cohort analyses

For our exploratory objective D1 cohort analyses, we will follow the new users from the index date until the earliest occurrence of the first outcome event of interest, death, disenrollment from the health plan, end of medical benefit, the study end date or 1 year of patient follow-up. For our exploratory objective D2 cohort analyses, we will follow individuals from the date of the indication for Ig use until the earliest occurrence of the first outcome event of interest (arterial TEE in analyses of this outcome, venous TEE in analyses of this outcome), death, disenrollment from the health plan, end of medical benefit, or study end date. The timeline will be calendar time. At each time when a TEE occurs, we will examine the hazard (i.e. risk) of TEE in relation to time-since-most-recent-Ig-treatment. The reference group will be the individuals who – at that time – had never been exposed to Ig.

H. STATISTICAL ANALYSES

1. Self-controlled analyses

The primary and secondary objectives will be addressed using a self-controlled risk interval design that compares risk during a post-exposure risk interval (days 0-2 for arterial outcomes, days 0-13 for venous outcomes) versus risk during a two-week comparison interval (days 14-27 for both types of outcomes). The risk and control intervals are diagrammed below for analyses of arterial outcomes (Figure **3** and Figure **4**) and venous outcomes (Figure 5 and Figure **6**), after an episode of IVIG treatment that is delivered on a single day (Figure **3** and Figure 5) or multiple days (Figure 4 and Figure **6**). The target effect for estimation is the relative risk, which will be estimated using a simple logistic regression model.

Figure 3. Risk Windows for Arterial Events, Single Dose

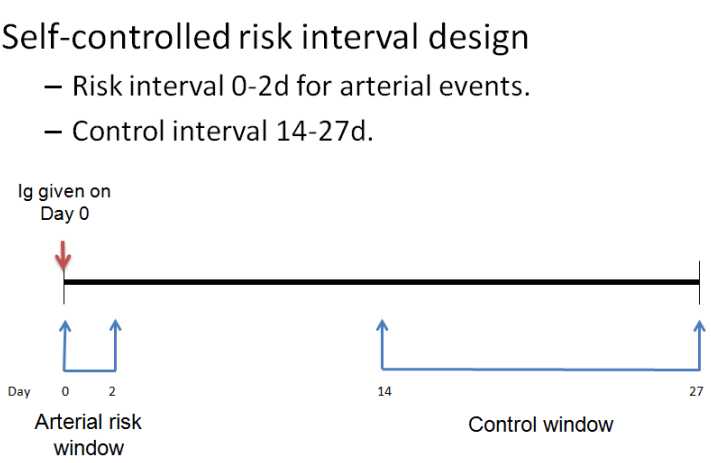


Figure 4. Risk Windows for Arterial Events, Multiple Doses

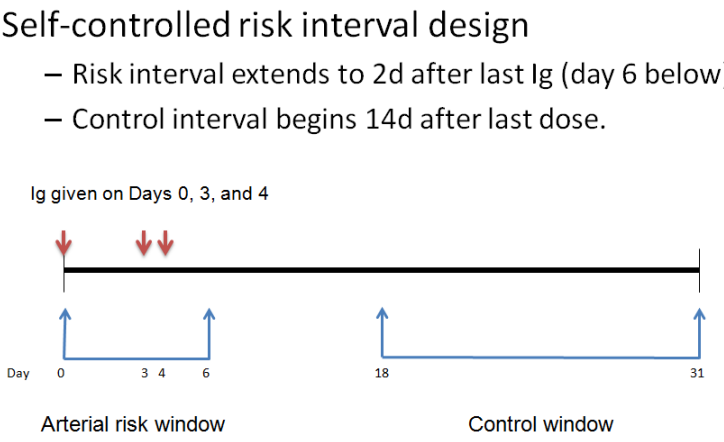
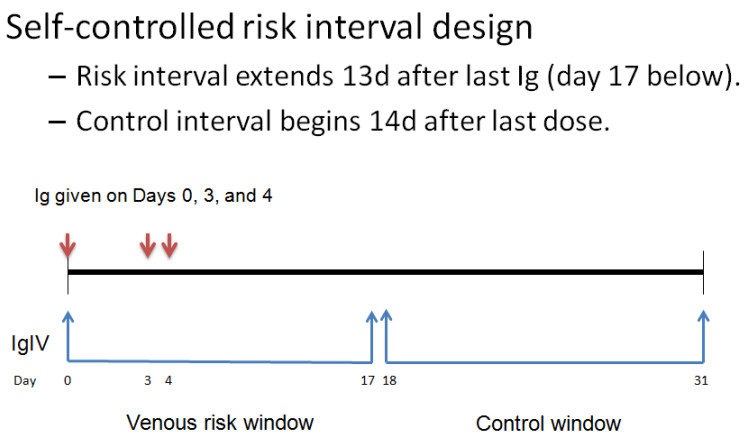


Figure 5. Risk Windows for Venous Events, Single Dose

Figure 6. Risk Windows for Venous Events, Multiple Doses



With the proposed self-controlled risk interval method, inference about the relative risk is informed only by Ig-treated individuals who had an outcome event during the risk or control interval. It will be feasible to chart review all (or nearly all) such individuals, and so our relative risk estimate will be based entirely on cases whose treatment and outcome information has been chart-confirmed.

If Ig treatment is safe and our risk and control intervals were equal in duration, then we would expect equal numbers of TEE during the risk and control intervals. However, for arterial outcomes the length of our risk interval is usually 2.5 days (assuming only a half-day of follow-up available on day 0, the day of exposure); the expected odds would be 2.5 to 14 that an arterial event occurred in the risk interval rather than the control interval, if Ig treatment poses no additional risk of TEE. For venous events the risk interval is usually 13.5 days and so among all venous events during the four weeks post-Ig, the expected odds that the TEE is in the risk interval would be 13.5 to 14.

The relative risk of TEE will be estimated by the odds ratio: the ratio of observed to expected odds of TEE occurring in the risk interval. For two-day and three-day treatment episodes the duration of the risk interval will be longer, as described above, and the expected odds will be the ratio of the risk interval length to the control interval length. For our primary analyses, TEE outcomes during the 4 weeks post-IVIg will be rare enough (less than 1 or 2% of treatment episodes) that it will be reasonable to examine first events only without attenuating the expected odds of TEE during the control interval. Under the null hypothesis, then, the expected odds that a first heart attack (after a 1-day Ig treatment) was in the risk interval versus control interval are 2.5 to 14 = .1786. If, for example, we actually find 100 in the risk interval and 100 in the control interval, then our relative risk estimate will be 1.0 / (2.5/14) = 5.6 (95% confidence interval: 4.2 – 7.4, to be estimated by logistic regression as described below).

The data will include one record for each chart-confirmed Ig-exposed case for whom a TEE occurred during either the risk interval or the control interval. The dependent variable will be coded 1 if the TEE was in the risk interval, 0 if in the control interval. The primary analyses will have no independent variables – only an offset which will specify the expected log odds of being in the risk interval. For most individuals this offset will amount to the log of 2.5/14 =-1.72 for analyses of arterial outcomes, but it will be somewhat higher if Ig treatment was planned for two or three consecutive days. The coefficient of the intercept will be exponentiated to estimate the odds ratio. The odds ratio is a reasonable estimator

of the relative risk in this relatively rare disease (< .5% of people who get Ig will have a TEE in the next four weeks).

This simple logistic regression model will yield the identical relative risk estimate, confidence interval, and hypothesis test as would a self-controlled case series analysis done by conditional Poisson regression, assuming both types of models are fit to data on the first outcome event per individual, including only events that occurred during the risk or control interval.

The same simple logistic regression will be used to examine the composite outcome of arterial or venous TEE. The other secondary objectives and exploratory objectives using chart confirmed data will be addressed by separate analyses in subgroups defined by product, dose, indication, history of TEE, decile of disease risk score, days since treatment (day 0 versus the control period, day 1 versus the control period, and day 2 versus the control period), treatment episode number, and calendar year (2006-2010 versus 2011-2012). To test the statistical significance of differences among subgroups in the relative risk of TEE, binary subgroup indicators will be added to the simple logistic regression model described above.

For venous events, Table 2 suggests that risk may be especially elevated during the first few days of the 13.5 day risk interval. If this pattern remains after chart review, our planned secondary analyses (which will also be informed only by chart-confirmed cases) would permit us to suggest that the risk of venous TEE is substantially elevated only during the early days of the risk interval.

Risk differences will be calculated by subtracting the numbers of TEE outcomes expected during the arterial and venous risk intervals from the numbers that are observed. For example, if after chart review we find an average of four arterial events per day during the control interval, then a total of 10 arterial events would be expected during the 2.5 day risk interval. If there 78 arterial events observed during the post-IVIg risk interval (as in Table 2), and also chart-confirmed, then our estimate of the risk difference would be 78 – 10 = 68. In 29,000 new users of IVIg, this would amount to 2.3 arterial TEE per 1,000 new users of IVIg.

2. Exploratory cohort analyses

a. Stratified Cox regression will be used for the exploratory analyses of the trajectory of TEE risk throughout the follow-up available after treatment. These analyses will include eligible new users of IM, SC or IV Ig with a recognized indication for Ig use (defined in Appendix A). The timeline will be calendar time. Analyses will be stratified by decile of the disease risk score and Data Partner. The Cox regression model will assess TEE risk in relation to time-since-Ig-exposure, examining risk sets anchored to calendar time: on each calendar day that an outcome event occurs in an Ig-treated individual, a risk set is formed that is comprised of all Ig-treated individuals who are in the same stratum and are at risk of a first post-Ig TEE. The covariates in the model will include time intervals since most recent Ig treatment: days 0-2, days 3-13, days 14-27, days 28-90, days 91-180, and days 181-365. Thus, within risk sets comprised of similar Ig-exposed individuals who were all at risk on the same calendar date when a TEE occurred, we examine how time-since-Ig-exposure is related to who it was—within the risk set –who experienced a TEE on that calendar date. To examine subgroups and test interactions, we will also include interaction terms in the stratified Cox regression models, interacting the time intervals since Ig exposure with indicators of subgroups. Because the exploratory analyses will include data not validated or augmented by chart review, we

will only be able to examine subgroups, such as individuals at highest risk for TEE or individuals with a specific indication for Ig treatment, individuals with SC or IM vs IVIg– identifiable from the electronic data. Sensitivity analyses will adjust the outcome definition from the claims-based definition that includes any inpatient diagnoses in a primary or unspecified position to a more restrictive definition based on the positive predictive values determined through the medical record review. The exploratory cohort analysis will consider indication as a proxy for dose due to the difficulty inferring dose from administrative data. Though we recognize the limitations of this as a proxy, it is expected that the majority of individuals with specific indications will receive doses in line with published reports of use in those indications.

b. The exploratory analyses including individuals who are untreated despite having an indication for Ig will also be done by stratified Cox regression. Individuals with recognized Ig indications will be identified from codes in Appendix A and the frequency distribution of these indications tabulated for descriptive purposes. As in the exploratory analyses described above, the timeline will be calendar time and analyses will be stratified by decile of the disease risk score and Data Partner. The simplest exploratory model will include a binary indicator of Ig treatment (ever-exposed versus never-exposed) as of the date of the TEE anchoring the risk set; additional models will compare the hazard of TEE during each of the time intervals post-treatment (0-2 days, 3-13 days, etc.) to a reference group comprised of the individuals who were never-treated as of the calendar day of the TEE anchoring the risk set. The "trajectory" of TEE incidence will be examined over calendar time as well as time-since Ig exposure. Calendar time and time-since-exposure will both be examined in discrete periods before considering linear trends. Special attention will be given to whether any IVIg effects on risk were reduced during the 2011-2012 period (after Ig products may have been modified). More generally, these exploratory analyses will provide context for interpreting the results of our primary analyses: if we find differences in risk between days 0-2 and days 14-27, the exploratory analyses will yield evidence regarding whether it is day 0-2 period or the day 14-27 period which differs in risk from other observable periods in Ig-exposed individuals and in other individuals with diagnoses indicating possible eligibility for Ig treatment.

c. The exposure and endpoint definitions used in the exploratory cohort analyses will be informed by the results of the chart reviews conducted for the primary self-controlled analyses. For example, if the validity of principal-position inpatient TEE diagnoses is found to be substantially higher than that of position-unspecified inpatient TEE diagnoses, we may restrict the endpoint definition to the former in the exploratory cohort analyses. In addition, if the dates associated with inpatient Ig procedure records (typically listed as the admission date in the administrative data) are found to be imprecise, we may restrict the exposure definition to outpatient Ig treatment records in the exploratory cohort analyses, since one of the primary goals of these analyses is to assess the relationship between time-since-Ig-treatment and TEE risk.

3. Disease risk score

This score is derived by Cox regression, examining TEE risk (specified as time-to-TEE) in relation to age, sex, and the healthcare utilization and diagnoses and treatments received in the baseline period in a cohort of Ig-untreated patients with a recognized indication for Ig use. The disease risk score (DRS) will be the linear predictor (xbeta) yielded by the fitted Cox model. The Cox model will be fitted separately at each of the participating data partners. A linear predictor will be calculated for each patient in the self-controlled and exploratory cohort analyses based on each of the DRS models, and these linear

predictors will be averaged with inverse-variance weighting to obtain a single DRS for each patient. Separate DRS models will be fitted for the arterial TEE and venous TEE endpoints. The disease risk scores will used in two ways: (a) to examine whether any of the IVIg effects that may be found in our primary self-controlled analyses are larger (or smaller) in patients who are at higher (or lower) levels of risk for TEE, and also (b) to adjust for potential confounders in our exploratory cohort analyses (which need such adjustment more than our primary self-controlled analyses).

I. PRIMARY ANALYSES OF POOLED DATA AND EXPLORATORY ANALYSES OF DATA DISTRIBUTED ACROSS DATA PARTNERS

The primary analyses will be done on pooled data, which will only include information on the chart-validated exposed cases (who had a TEE within weeks of receiving Ig). The exploratory cohort analyses, and the analyses yielding the algorithm for the disease risk score, will be done separately at each Data Partner on the distributed data. For the exploratory cohort analyses (as described above), only de-identified risk set level data (rather than individual patient-level data) will be pooled to fit the stratified Cox models. We can obtain the same results from the de-identified risk set level data as we would have obtained had we pooled all the individual data.[38]

J. THROMBOEMBOLIC EVENTS AND IMMUNOGLOBULIN EXPOSURE VALIDATION

TEE cases identified in the MSDD that occur in the risk or control windows following an Ig dose will undergo medical record review. More than one chart per case may be requested for review because information about the exposure and outcome may be recorded in different charts. Thus it will be necessary to review and rank the claims history of each selected patient to identify encounters that are mostly likely to produce the most definitive exposure and outcome information. For these reasons, the project will request individual patient-level data from the MSDD for a modest number of patients who experienced TEE soon after IVIg. The data will not include names, health plan numbers, hospital names or other specific identifiers, and will only include information about relevant diagnoses, procedures, and treatments, as well as demographics such as age and sex.

Charts will be reviewed to confirm the event, obtain information about the onset of the event, confirm the exposure and dates of exposure, and obtain information about the details of exposure (dose, infusion rate, specific product, route of administration). Information on indication for Ig use, history of prior events, and major cardiovascular and thrombotic risk factors will also be collected. Direct patient identifiers, such as name and health plan number, will be redacted before the charts are sent to the MSOC. Actual service dates recorded in the charts will not be redacted since such information is deemed necessary to validate the exposure and outcome, and manual transformation of the dates into relative dates is thought to be cost-prohibitive and error-prone.

For exposure verification, the dates and times of all exposures within a specific time window will be recorded, including the date and time of the first exposure. The average infusion rate will be calculated by using data on dose, time infusion began and ended, and patient weight. Ig infusions are often given with an increasing infusion rate, based on the patient's ability to tolerate an increasing rate. It is not expected that this titration of infusion rate will be consistently available, even in nurse notes. Thus, the time at the start and end of the infusion would give an average rate but this would not be the actual rate. The indication for Ig (e.g., motor nerve defect) will be recorded for each patient as well as the specific brand of Ig if available. The planned regimen including the planned dose, planned number of

days per episode, and planned number of episodes, will be recorded as well as any differences between the planned regimen and the administered regimen. For people planned for multiple treatment episodes, the planned number of days between episodes will also be collected. This will allow assignment of a shorter control window if the planned start of the next treatment episode is within the 27-day window. The treatment episode number will also be collected when there have been multiple treatment episodes. Other data collected on the exposure will include location of administration (e.g., inpatient, outpatient infusion suite, home), patient demographics (e.g., age, race), and administration of other therapeutics such as anticoagulants or thrombolytics.

For case validation, to be considered a definite event, our primary ischemic stroke definition requires rapid onset of a persistent neurologic deficit attributable to central nervous system infarction (including stroke occurring during or resulting from a procedure), i.e. brain, spinal cord, or retinal cell death attributable to ischemia. The deficit must not be known to be secondary to brain trauma, tumor, infection, or other cause. The deficit must last more than 24 hours, unless death supervenes or there is a demonstrable lesion compatible with acute stroke on computed tomography (CT) or magnetic resonance imaging (MRI) scan. A deficit that lasts more than 24 hours, but for which there is no evidence of stroke by imaging or other identified cause, will be considered a stroke.[39] A physician note that clearly indicates the physician reviewed the primary information can qualify as a definite stroke. A stroke will be defined as procedure-related if it occurs within 24 hours after any procedure or within 30 days after a cardioversion or invasive cardiovascular procedure.

Table 4 displays the requirements to be considered a definite AMI for our primary case definition;[40] Table 5 displays the corresponding definitions for PE and DVT.[41] DVT of the upper extremity will be excluded, as central venous catheters present a potential source of time-varying confounding.

Cerebral venous thrombosis (CVT) validation will require a history of symptoms consistent with CVT and objective evidence of CVT obtained by imaging or autopsy. Symptoms include headaches, vomiting, decreased level of consciousness, focal motor deficits, trouble speaking or understanding speech, vision problems, loss of coordination, problems with balance, seizures, psychosis, or other neurologic signs. Typical imaging modalities to diagnose CVT are MRI or CT, including venography using either modality. Other diagnostic modalities include cerebral angiography, cerebral venography, and ultrasound.[42]

Table 4. Acute Myocardial Infarction Case Validation Criteria*

Cardiac Enzyme Interpretation (see sub-table below)				
	Abnormal	**Equivocal**	**Incomplete**	**Normal**
ECG Pattern/Symptoms				
Cardiac pain present:				
Evolving, diagnostic ECG: Evolving Q wave and evolving ST-T abnormalities	Definite MI	Definite MI	Definite MI	Definite MI
Positive ECG: Equivocal Q wave evolution with ST-T depression/inversion; or evolving ST-T elevation alone; or new left bundle branch block	Definite MI	Definite MI	Probable MI	No MI
Nonspecific ECG: evolution of minor ST-T depression/inversion or minor Q-wave evolution alone and not	Definite MI	Probable MI	No MI	No MI

Cardiac Enzyme Interpretation (see sub-table below)				
classified above				
ECG negative for ischemia: Normal ECG, other ECG, or ECG absent	Definite MI	No MI	No MI	No MI
Cardiac pain absent:				
Evolving, diagnostic ECG: Evolving Q wave and evolving ST-T abnormalities	Definite MI	Definite MI	Definite MI	Probable MI
Positive ECG: Equivocal Q wave evolution with ST-T depression/inversion; or evolving ST-T elevation alone; or new left bundle branch block	Definite MI	Probable MI	No MI	No MI
Nonspecific ECG: evolution of minor ST-T depression/inversion or minor Q-wave evolution alone and not classified above	Probable MI	No MI	No MI	No MI
ECG negative for ischemia: Normal ECG, ECG absent or unreadable	No MI	No MI	No MI	No MI

	Interpretation		
Cardiac Enzyme	**Abnormal**	**Equivocal**	**Normal**
CK-MB (highest value)	$\geq$99th percentile URL	>ULN and <99th percentile URL	WNL
Troponin (highest value)	$\geq$99th percentile URL	>ULN and <99th percentile URL	WNL
CK (no MB available- consider highest value)	N/A	$\geq$99th percentile URL	WNL

*A physician diagnosis that reports the criteria used for the diagnosis can qualify as a definite or probably MI.

Table 5. Venous Thromboembolism Case Validation Criteria*

	Pulmonary Embolism	**Deep Vein Thrombosis**
Definite	Confirmed by pulmonary angiography, spiral CT scan, MRI scan or pathology	Confirmed by conventional venography, compression/ duplex ultrasound, CT scan/CT angiography or pathology
Probable	If above tests not performed or were indeterminate, but ventilation-perfusion scan findings were of high probability	If above tests not performed or were indeterminate, but impedance plethysomography, radionucleotide venography, or radiolabelled fibrinogen scan test results were reported as positive
Possible	If all of the above tests were not performed or were indeterminate and 2 of the following criteria were satisfied: medical record indicates physician- diagnosed acute DVT, signs or symptoms of acute DVT were documented and the patient underwent therapy with anticoagulants, or an IVC filter was placed.	If all of the above tests were not performed or were indeterminate and 2 of the following criteria were satisfied: medical record indicates physician-diagnosed acute DVT, signs or symptoms of acute DVT were documented and the patient underwent therapy with anticoagulants, or an IVC filter was placed.

*A physician diagnosis that reports the criteria used for the diagnosis can qualify as a definite or probable VTE.

IV. POWER CALCULATION

From Table 2, we estimate that a total of 131 potential arterial events will be found in the electronic data during the risk or control intervals after IVIg (this estimate of 131 is yielded by subtracting an estimate of the number of events during days 3-13). If all 131 are confirmed by chart review, we will have 80% power to detect a relative risk of 1.65, using a one-sided test with alpha = 0.05. If 98 (75%) of 131 are confirmed, then our least detectable relative risk will be 1.78. The test statistic will be the Wald Z-score yielded by the logistic regression (described above in section III.H.1): it is the estimate of the log odds ratio divided by its standard error.

Table 2 indicates 179 venous events during the risk or control intervals after IVIg treatment. This number is 37% higher than the number of potential arterial events. However, we expect that a lower percentage of venous events than arterial events will be confirmed by chart review. Overall, we expect the number of chart-confirmed venous events to be similar to the number of chart confirmed arterial events. Thus, for each of our primary analyses we expect the least detectable relative risk to be near 1.7 or 1.8.

If the PPV of the chart-reviewed events is found to be no different in the risk interval than in the control interval, then Table 2 suggests that our primary relative risk estimates will be substantially higher than the least detectable relative risks of 1.7 or 1.8. For example, a relative risk of 8.2 for arterial events post-IVIg can be estimated from Table 2 (after accounting for the washout period from day 3 to day 13). If all 131 potentially informative arterial events are chart-confirmed, the corresponding 95% confidence interval would extend from 5.8 to 11.7.

V. APPENDIX

A. APPENDIX A: DEFINITIONS OF INDICATIONS FOR IMMUNOGLOBULIN USE

Below is a table displaying administrative diagnosis and procedure codes associated with indicated conditions for intravenous, subcutaneous or intramuscular immunoglobulin use. Table A 1 groups indicated conditions into the following categories: (1) inflammatory and/or autoimmune conditions, (2) immune deficiency, (3) treatment of acute infection, (4) pre- or post-exposure prophylaxis against infection, (5) hematopoietic stem cell or bone marrow transplantation, and (6) other. In order to be included in the primary self-controlled analyses, patients were required to have had an Ig indication observed in the interval [proximate Ig date -183 days, proximate Ig date +1 day]. We will attempt to confirm the route of administration and indication in each reviewed case for the objectives using chart confirmed data, though the ability to do this is dependent upon adequate documentation in the patient chart.

FDA-approved and other generally recognized indications for Ig use[43] (Orange, 2006) have a "Y" in the column "Recognized Indication." To be eligible for inclusion in the disease risk score cohorts and exploratory cohort analyses, we required that patients have at least one recognized indication for Ig use recorded during the 183-day lookback period.

Table A 1 also includes the typical dose of Ig administered for each indication, and its associated diagnosis code and description. The majority of literature on Ig use in acute conditions, such as inflammatory disorders, reports administration of IVIg at a total dose of > 1 g/kg in a treatment episode, which often spans multiple days. In contrast, the labeled doses of IVIg for primary immune deficiency ranges from 200-800 mg/kg, typically at 3-4 week intervals. Similarly, the labeled IVIg dose for secondary immune deficiency in products labeled for that condition is 400 mg/kg every 3 to 4 weeks. IVIg is also administered in treatment episodes using doses lower than 1 g/kg for some preventive and chronic indications. Thus, 1g/kg was chosen as a convenient cutoff for categorizing dose into high, low, and unclassifiable (H, L, and U, respectively, in Table A 1 below).

Table A 1. Indicated Conditions for Ig Use: Categorization and Associated Administrative Diagnosis/Procedure Codes

Code type*	Code†	Description	Category	Recognized indication	Dose‡
DX09	0363	Waterhouse-Friderichsen syndrome, meningococcal	3. Active infection	N	U
DX09	042	Human immunodeficiency virus infection	2. Immune deficiency	Y	L
DX09	052	Chickenpox	3. Active infection	N	U
DX09	056	Rubella	3. Active infection	N	U

Code type*	Code†	Description	Category	Recognized indication	Dose‡
DX09	0664	West Nile fever	3. Active infection	N	H
DX09	0785	Cytomegaloviral disease	3. Active infection	N	L
DX09	07983	Parvovirus B19	3. Active infection	N	H
DX09	084	Malaria	3. Active infection	N	L
DX09	1361	Bechet's syndrome	1. Autoimmune/inflammatory condition	N	H
DX09	138	Late effects of acute poliomyelitis	6. Other	N	H
DX09	1640	Malignant neoplasm of thymus	6. Other	N	H
DX09	172	Malignant melanoma of skin	6. Other	N	H
DX09	176	Kaposi's sarcoma	6. Other	N	H
DX09	20190	Hodgkin's disease, unspecified type, extranodal and solid organ types	6. Other	N	H
DX09	20208	Nodular lymphoma involving lymph nodes of multiple sites	6. Other	N	H
DX09	20210	Mycosis fungoides, unspecified site, extranodal and solid organ sites	6. Other	N	H
DX09	20280	Other malignant lymphomas, unspecified site, extranodal and solid organ sites	6. Other	N	H
DX09	20281	Other malignant lymphomas involving lymph nodes of head, face, and neck	6. Other	N	H
DX09	20300	Multiple myeloma, without mention of having achieved remission, failed remission	2. Immune deficiency	Y	U
DX09	20400	Lymphoid leukemia, acute, without mention of having achieved remission	6. Other	Y	L
DX09	20401	Lymphoid leukemia, acute, in remission	6. Other	Y	L
DX09	20402	Lymphoid leukemia, acute, in relapse	2. Immune deficiency	Y	L
DX09	2041	Chronic lymphoid leukemia	2. Immune deficiency	Y	L
DX09	20480	Other lymphoid leukemia, without mention of having achieved remission, failed remission	2. Immune deficiency	Y	L
DX09	20490	Unspecified lymphoid leukemia, without mention of having achieved remission, failed remission	2. Immune deficiency	Y	L

Code type*	Code†	Description	Category	Recognized indication	Dose‡
DX09	20501	Myeloid leukemia, acute, in remission	6. Other	Y	L
DX09	20510	Myeloid leukemia, chronic, without mention of having achieved remission, failed remission	6. Other	Y	L
DX09	20820	Leukemia of unspecified cell type, subacute, without mention of having achieved remission	2. Immune deficiency	Y	L
DX09	20890	Unspecified leukemia, without mention of having achieved remission	2. Immune deficiency	Y	L
DX09	23871	Essential thrombocythemia	6. Other	N	U
DX09	23875	Myelodysplastic syndrome, unspecified	6. Other	Y	L
DX09	23877	Post-transplant lymphoproliferative disorder	6. Other	Y	L
DX09	23879	Other lymphatic and hematopoietic tissues	6. Other	N	U
DX09	24200	Toxic diffuse goiter without mention of thyrotoxic crisis or storm	1. Autoimmune/inflammatory condition	Y	H
DX09	2580	Polyglandular activity in multiple endocrine adenomatosis	1. Autoimmune/inflammatory condition	N	H
DX09	27502	Hemochromatosis due to repeated RBC transfusions	1. Autoimmune/inflammatory condition	N	H
DX09	27503	Other hemochromatosis	1. Autoimmune/inflammatory condition	N	H
DX09	27786	Peroxisomal disorders	6. Other	N	H
DX09	27787	Disorders of mitochondrial metabolism	6. Other	N	L
DX09	279	Disorders involving the immune mechanism	2. Immune deficiency	Y	L
DX09	2790	Deficiency of humoral immunity	2. Immune deficiency	Y	L
DX09	2791	Deficiency of cell-mediated immunity	2. Immune deficiency	Y	L
DX09	2792	Combined immunity deficiency	2. Immune deficiency	Y	L
DX09	2793	Unspecified immunity deficiency	2. Immune deficiency	Y	L
DX09	2794	Autoimmune disease, not elsewhere classified	1. Autoimmune/inflammatory condition	N	L
DX09	2795	Graft-versus-host disease	1. Autoimmune/inflammatory condition	Y	H
DX09	2830	Autoimmune hemolytic anemias	1. Autoimmune/inflammatory condition	Y	H
DX09	28311	Hemolytic-uremic syndrome	1. Autoimmune/inflammatory condition	N	H
DX09	28401	Constitutional red blood cell aplasia	1. Autoimmune/inflammatory condition	N	H

Code type*	Code†	Description	Category	Recognized indication	Dose‡
DX09	2849	Aplastic anemia, unspecified	1. Autoimmune/inflammatory condition	N	H
DX09	2864	von Willebrand's disease	1. Autoimmune/inflammatory condition	N	H
DX09	28652	Acquired hemophilia	1. Autoimmune/inflammatory condition	Y	H
DX09	28659	Other hemorrhagic disorder due to intrinsic circulating anticoagulants, antibodies, or inhibitors	1. Autoimmune/inflammatory condition	N	H
DX09	2870	Allergic purpura	1. Autoimmune/inflammatory condition	N	H
DX09	2873	Primary thrombocytopenia	1. Autoimmune/inflammatory condition	N	H
DX09	28730	Primary thrombocytopenia, unspecified	1. Autoimmune/inflammatory condition	N	H
DX09	28731	Immune thrombocytopenic purpura	1. Autoimmune/inflammatory condition	Y	H
DX09	28732	Evans' syndrome	1. Autoimmune/inflammatory condition	Y	H
DX09	2874	Secondary thrombocytopenia	1. Autoimmune/inflammatory condition	N	H
DX09	28741	Posttransfusion purpura	1. Autoimmune/inflammatory condition	Y	H
DX09	2875	Thrombocytopenia, unspecified	1. Autoimmune/inflammatory condition	N	H
DX09	2880	Neutropenia (excluding 288.09, see below)	6. Other	N	H
DX09	28809	Other neutropenia (agranulocytosis, immune, toxic)	1. Autoimmune/inflammatory condition	N	H
DX09	2881	Functional disorders of polymorphonuclear neutrophils	6. Other	N	H
DX09	2884	Hemophagocytic syndromes	1. Autoimmune/inflammatory condition	N	H
DX09	2891	Chronic lymphadenitis	1. Autoimmune/inflammatory condition	N	H
DX09	2893	Lymphadenitis, unspecified, except mesenteric	1. Autoimmune/inflammatory condition	N	H
DX09	28984	Heparin-induced thrombocytopenia (HIT)	1. Autoimmune/inflammatory condition	N	H
DX09	299	Pervasive developmental disorders	6. Other	N	L
DX09	32361	Infectious acute disseminated encephalomyelitis	1. Autoimmune/inflammatory condition	Y	H
DX09	32381	Other causes of encephalitis and encephalomyelitis	1. Autoimmune/inflammatory condition	Y	H
DX09	3310	Alzheimer's disease	1. Autoimmune/inflammatory condition	N	H
DX09	3332	Myoclonus	1. Autoimmune/inflammatory condition	N	H
DX09	33391	Stiff-man syndrome	1. Autoimmune/inflammatory condition	Y	H
DX09	33520	Amyotrophic lateral sclerosis	1. Autoimmune/inflammatory condition	N	H

Code type*	Code†	Description	Category	Recognized indication	Dose‡
DX09	340	Multiple sclerosis	1. Autoimmune/inflammatory condition	Y	H
DX09	3483	Encephalopathy, not classified elsewhere	1. Autoimmune/inflammatory condition	N	H
DX09	3535	Neuralgic amyotrophy	1. Autoimmune/inflammatory condition	N	H
DX09	3570	Acute infectious polyneuritis	1. Autoimmune/inflammatory condition	Y	H
DX09	3571	Polyneuropathy in collagen vascular disease	1. Autoimmune/inflammatory condition	Y	H
DX09	3572	Polyneuropathy in diabetes	1. Autoimmune/inflammatory condition	N	H
DX09	35781	Chronic inflammatory demyelinating polyneuritis	1. Autoimmune/inflammatory condition	Y	H
DX09	35782	Critical illness polyneuropathy	1. Autoimmune/inflammatory condition	N	H
DX09	3579	Unspecified inflammatory and toxic neuropathy	1. Autoimmune/inflammatory condition	N	H
DX09	3580	Myasthenia gravis	1. Autoimmune/inflammatory condition	Y	H
DX09	3583	Lambert-Eaton syndrome	1. Autoimmune/inflammatory condition	Y	H
DX09	35971	Inclusion body myositis	1. Autoimmune/inflammatory condition	N	H
DX09	3630	Focal chorioretinitis and focal retinochoroiditis	1. Autoimmune/inflammatory condition	Y	H
DX09	37612	Orbital myositis	1. Autoimmune/inflammatory condition	N	L
DX09	3773	Optic neuritis	1. Autoimmune/inflammatory condition	N	H
DX09	37855	External ophthalmoplegia	6. Other	N	L
DX09	37959	Other irregularities of eye movements (opsoclonus)	1. Autoimmune/inflammatory condition	Y	H
DX09	390	Acute rheumatic fever; Chronic rheumatic heart disease	1. Autoimmune/inflammatory condition	N	H
DX09	391	Acute rheumatic fever; Chronic rheumatic heart disease	1. Autoimmune/inflammatory condition	N	H
DX09	392	Acute rheumatic fever; Chronic rheumatic heart disease	1. Autoimmune/inflammatory condition	N	H
DX09	393	Acute rheumatic fever; Chronic rheumatic heart disease	1. Autoimmune/inflammatory condition	N	H
DX09	394	Acute rheumatic fever; Chronic rheumatic heart disease	1. Autoimmune/inflammatory condition	N	H
DX09	395	Acute rheumatic fever; Chronic rheumatic heart disease	1. Autoimmune/inflammatory condition	N	H
DX09	396	Acute rheumatic fever; Chronic rheumatic heart disease	1. Autoimmune/inflammatory condition	N	H
DX09	397	Acute rheumatic fever; Chronic rheumatic heart disease	1. Autoimmune/inflammatory condition	N	H
DX09	398	Acute rheumatic fever; Chronic rheumatic heart disease	1. Autoimmune/inflammatory condition	N	H

Code type*	Code†	Description	Category	Recognized indication	‡
DX09	420	Acute pericarditis	1. Autoimmune/inflammatory condition	N	H
DX09	422	Acute myocarditis	1. Autoimmune/inflammatory condition	Y	H
DX09	423	Other diseases of pericardium	1. Autoimmune/inflammatory condition	N	H
DX09	42491	Endocarditis in diseases classified elsewhere	1. Autoimmune/inflammatory condition	Y	H
DX09	425	Cardiomyopathy	1. Autoimmune/inflammatory condition	N	H
DX09	428	Heart failure	1. Autoimmune/inflammatory condition	N	H
DX09	4460	Polyarteritis nodosa	1. Autoimmune/inflammatory condition	N	H
DX09	4461	Acute febrile mucocutaneous lymph node syndrome [MCLS]	1. Autoimmune/inflammatory condition	Y	H
DX09	4464	Wegener's granulomatosis	1. Autoimmune/inflammatory condition	N	H
DX09	52801	Mucositis (ulcerative) due to antineoplastic therapy	6. Other	N	L
DX09	555	Regional enteritis	1. Autoimmune/inflammatory condition	N	H
DX09	57142	Autoimmune hepatitis	1. Autoimmune/inflammatory condition	N	H
DX09	580	Acute glomerulonephritis	1. Autoimmune/inflammatory condition	N	H
DX09	581	Nephrotic syndrome	1. Autoimmune/inflammatory condition	Y	H
DX09	582	Chronic glomerulonephritis	1. Autoimmune/inflammatory condition	N	H
DX09	583	Nephritis and nephropathy, not specified as acute or chronic	1. Autoimmune/inflammatory condition	Y	H
DX09	6475	Rubella complicating pregnancy	3. Active infection	Y	L
DX09	6553	Suspected damage to fetus from viral disease in the mother	3. Active infection	Y	L
DX09	68601	Pyoderma gangrenosum	1. Autoimmune/inflammatory condition	N	H
DX09	691	Atopic dermatitis and related conditions	1. Autoimmune/inflammatory condition	N	H
DX09	6944	Pemphigus	1. Autoimmune/inflammatory condition	N	H
DX09	6945	Pemphigoid	1. Autoimmune/inflammatory condition	N	H
DX09	6946	Benign mucous membrane pemphigoid	1. Autoimmune/inflammatory condition	N	H
DX09	6948	Other specified bullous dematoses	1. Autoimmune/inflammatory condition	N	H
DX09	6951	Erythema multiforme	1. Autoimmune/inflammatory condition	Y	H
DX09	6954	Lupus erythematosus	1. Autoimmune/inflammatory condition	Y	H

Code type*	Code†	Description	Category	Recognized indication	Dose‡
DX09	696	Psoriasis and similar disorders	1. Autoimmune/inflammatory condition	N	H
DX09	7018	Other specified hypertrophic and atrophic conditions of the skin	1. Autoimmune/inflammatory condition	N	H
DX09	70409	Other alopecia	6. Other	N	L
DX09	708	Urticaria	1. Autoimmune/inflammatory condition	N	H
DX09	7100	Systemic lupus erythematosus	1. Autoimmune/inflammatory condition	Y	H
DX09	7101	Systemic sclerosis	1. Autoimmune/inflammatory condition	N	H
DX09	7102	Sicca syndrome	1. Autoimmune/inflammatory condition	N	H
DX09	7103	Dermatomyositis	1. Autoimmune/inflammatory condition	Y	H
DX09	7104	Polymyositis	1. Autoimmune/inflammatory condition	Y	H
DX09	7108	Other specified diffuse diseases of connective tissue	1. Autoimmune/inflammatory condition	N	H
DX09	7109	Unspecified diffuse connective tissue disease	1. Autoimmune/inflammatory condition	N	H
DX09	7112	Arthropathy in Behcet's syndrome	1. Autoimmune/inflammatory condition	N	H
DX09	7140	Rheumatoid arthritis	1. Autoimmune/inflammatory condition	N	H
DX09	7143	Juvenile chronic polyarthritis	1. Autoimmune/inflammatory condition	N	H
DX09	7281	Muscular calcification and ossification	6. Other	N	U
DX09	7287	Other fibromatoses of muscle, ligament, and fascia	6. Other	N	U
DX09	72886	Necrotizing fasciitis	3. Active infection	N	H
DX09	75739	Other anomalies of skin (Other)	1. Autoimmune/inflammatory condition	N	H
DX09	7761	Transient neonatal thrombocytopenia	1. Autoimmune/inflammatory condition	Y	H
DX09	78071	Chronic fatigue syndrome	6. Other	N	U
DX09	99591	Systemic inflammatory response syndrome due to infectious process without acute organ dysfunction	3. Active infection	N	L
DX09	99592	Systemic inflammatory response syndrome due to infectious process with acute organ dysfunction	3. Active infection	N	L
DX09	9968	Complications of transplanted organ	3. Active infection	Y	H
DX09	99685	Complications of transplanted organ (bone marrow)	5. Hematopoietic stem cell/bone marrow transplant	Y	U

Code type*	Code†	Description	Category	Recognized indication	Dose‡
DX09	9997	Rh incompatibility reaction, not elsewhere classified	1. Autoimmune/inflammatory condition	N	U
DX09	V014	Contact with or exposure to rubella	4. Pre/post exposure infection prophylaxis	Y	L
DX09	V0171	Contact with or exposure to varicella	4. Pre/post exposure infection prophylaxis	Y	L
DX09	V0179	Contact with or exposure to other viral disease	4. Pre/post exposure infection prophylaxis	N	L
DX09	V042	Need for prophylactic vaccination and inoculation against measles alone	4. Pre/post exposure infection prophylaxis	Y	L
DX09	V043	Need for prophylactic vaccination and inoculation against rubella alone	4. Pre/post exposure infection prophylaxis	Y	L
DX09	V0489	Contact with or exposure to other viral disease	4. Pre/post exposure infection prophylaxis	N	L
DX09	V053	Need for prophylactic vaccination and inoculation against viral hepatitis	4. Pre/post exposure infection prophylaxis	N	L
DX09	V072	Prophylactic immunotherapy	2. Immune deficiency	Y	L
DX09	V1585	Exposure to potentially hazardous body fluids	4. Pre/post exposure infection prophylaxis	Y	U
DX09	V4281	Organ or tissue replaced by transplant, bone barrow	5. Hematopoietic stem cell/bone marrow transplant	Y	U
PX09	4100	Bone marrow transplant, not otherwise specified	5. Hematopoietic stem cell/bone marrow transplant	Y	U
PX09	4102	Allogeneic bone marrow transplant with purging	5. Hematopoietic stem cell/bone marrow transplant	Y	U
PX09	4103	Allogeneic bone marrow transplant without purging	5. Hematopoietic stem cell/bone marrow transplant	Y	U
PX09	4105	Allogeneic hematopoietic stem cell transplant without purging	5. Hematopoietic stem cell/bone marrow transplant	Y	U
PX09	4108	Allogeneic hematopoietic stem cell transplant	5. Hematopoietic stem cell/bone marrow transplant	Y	U
PXC4	38240	Hematopoietic progenitor cell (HPC) transplantation, allogeneic	5. Hematopoietic stem cell/bone marrow transplant	Y	U

Code type*	Code†	Description	Category	Recognized indication	Dose‡
PXC4	38242	Allogeneic lymphocyte infusion	5. Hematopoietic stem cell/bone marrow transplant	Y	U
PXHC	S2065	Pancreas/kidney transplant	1. Autoimmune/inflammatory condition	Y	H
PXHC	S2150	Allogeneic bone marrow transplant	5. Hematopoietic stem cell/bone marrow transplant	Y	U

*Code type abbreviations: DX09 = ICD-9-CM diagnosis code, PXC4 = Current Procedural Terminology 4 (CPT-4) procedure code, PXHC = Healthcare Common Procedure Coding System (HCPCS) code

†Decimal points removed from code field

‡Dose abbreviations: H = high dose (≥1 g/kg), L = low dose (< 1 g/kg), U = unclassified

B. APPENDIX B: LIST OF IMMUNOGLOBULIN EXPOSURE CODES

Below is a table displaying the details for immunoglobulin exposure codes we considered for this study.

Table B 1 includes the code type, drug product, route of administration, and description associated with each code. We have also considered and included NDC codes related to the ingredient "globulin, immune" as of August 2013, though they are not featured in the table. Please note that codes will be further evaluated prior to implementation. We may restrict exposure codes to route-specific CPT, HCPCS, and NDC codes to identify IVIg use for chart review, and further restrict to Ig users with plausible indications through associated diagnosis codes in claims data.

Table B 1. MS IVIG-TEE Codes for Ig Administration (excluding NDCs)

Code	Code Type	Drug Product	Route	Description
90281	CPT	Unspecified	Intramuscular	Immune globulin (Ig), human, for intramuscular use
90283	CPT	Unspecified	Intravenous	Immune globulin (IgIV), human, for intravenous use
90284	CPT	Unspecified	Subcutaneous	Immune globulin (SCIg), human, for use in subcutaneous infusions, 100 mg, each
90399	CPT	Unspecified	Unspecified	Unlisted immune globulin
C9270	HCPCS	Gammaplex	Intravenous	Injection, immune globulin (Gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1459	HCPCS	Privigen	Intravenous	Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1460	HCPCS	Unspecified	Intramuscular	Injection, gamma globulin, intramuscular, 1 cc
J1470	HCPCS	Unspecified	Intramuscular	Injection, gamma globulin, intramuscular, 2 cc
J1480	HCPCS	Unspecified	Intramuscular	Injection, gamma globulin, intramuscular, 3 cc
J1490	HCPCS	Unspecified	Intramuscular	Injection, gamma globulin, intramuscular, 4 cc
J1500	HCPCS	Unspecified	Intramuscular	Injection, gamma globulin, intramuscular, 5 cc
J1510	HCPCS	Unspecified	Intramuscular	Injection, gamma globulin, intramuscular, 6 cc
J1520	HCPCS	Unspecified	Intramuscular	Injection, gamma globulin, intramuscular, 7 cc
J1530	HCPCS	Unspecified	Intramuscular	Injection, gamma globulin, intramuscular, 8 cc
J1540	HCPCS	Unspecified	Intramuscular	Injection, gamma globulin, intramuscular, 9 cc

Code	Code Type	Drug Product	Route	Description
J1550	HCPCS	Unspecified	Intramuscular	Injection, gamma globulin, intramuscular, 10 cc
J1557	HCPCS	Gammaplex	Intravenous	Injection, immune globulin (Gammaplex), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1559	HCPCS	Hizentra	Subcutaneous	Injection, immune globulin (Hizentra), 100 mg
J1560	HCPCS	Unspecified	Intramuscular	Injection, gamma globulin, intramuscular, over 10 cc
J1561	HCPCS	Gamunex/ Gamunex-C/ Gammaked	Intravenous	Injection, immune globulin (Gamunex/Gamunex-C/ Gammaked), non-lyophilized (e.g., liquid), 500 mg
J1562	HCPCS	Vivaglobin	Subcutaneous	Injection, immune globulin (Vivaglobin), 100 mg. [Code effective date: 20080101]
J1563	HCPCS	Unspecified	Intravenous	Injection, immune globulin, intravenous, 1g
J1564	HCPCS	Unspecified	Intravenous	Injection, immune globulin, 10 mg
J1566	HCPCS	Unspecified	Intravenous	Injection, immune globulin, intravenous, lyophilized (e.g., powder), 500 mg
J1567	HCPCS	Unspecified	Intravenous	Injection, immune globulin, intravenous, non-lyophilized (e.g., liquid), 500 mg
J1568	HCPCS	Octagam	Intravenous	Injection, immune globulin (Octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1569	HCPCS	Gammagard Liquid	Intravenous	Injection, immune globulin (Gammagard Liquid), intravenous, non-lyophilized, (e.g., liquid), 500 mg
J1572	HCPCS	Flebogamma	Intravenous	Injection, immune globulin (Flebogamma), intravenous, non-lyophilized (e.g., liquid), 500 mg
J1599	HCPCS	Unspecified	Intravenous	Injection, immune globulin, intravenous, non-lyophilized (e.g., liquid), not otherwise specified, 500 mg
P9014	HCPCS	Unspecified	Intramuscular	Globulin, gamma, 1 mL
Q4087	HCPCS	Octagam	Intravenous	Injection, immune globulin (Octagam), intravenous, non-lyophilized (e.g., liquid), 500 mg

Code	Code Type	Drug Product	Route	Description
Q4088	HCPCS	Gammagard Liquid	Intravenous	Injection, immune globulin (Gammagard Liquid), intravenous, non-lyophilized, (e.g., liquid), 500 mg
Q4091	HCPCS	Flebogamma	Intravenous	Injection, immune globulin (Flebogamma), intravenous, non-lyophilized, (e.g., liquid), 500 mg
Q4092	HCPCS	Gamunex	Intravenous	Injection, immune globulin (Gamunex), intravenous, non-lyophilized (e.g., liquid), 500 mg
Q4097	HCPCS	Privigen	Intravenous	Injection, immune globulin (Privigen), intravenous, non-lyophilized (e.g., liquid), 500 mg
Q9941	HCPCS	Unspecified	Intravenous	Injection, immune globulin, intravenous, lyophilized, 1g
Q9942	HCPCS	Unspecified	Intravenous	Injection, immune globulin, intravenous, lyophilized, 10 mg
Q9943	HCPCS	Unspecified	Intravenous	Injection, immune globulin, intravenous, non-lyophilized, 1g
Q9944	HCPCS	Unspecified	Intravenous	Injection, immune globulin, intravenous, non-lyophilized, 10 mg
S9545	HCPCS	Unspecified	Intravenous	Administration of immune globulin, intravenously, in the home setting, including all nursing care, equipment, and supplies; per diem
9914	ICD-9	Unspecified	Unspecified	Injection or infusion of immunoglobulin

C. APPENDIX C: DIAGNOSIS CODES FOR SERIOUS THROMBOEMBOLIC EVENTS

Below is a table displaying the details for the diagnosis codes for serious thromboembolic events we considered for this study. Table C 1 includes the outcome class, outcome and ICD-9 code.

Table C 1. MS IVIG-TEE Diagnosis Codes for Serious Thromboembolic Events

Outcome Class	Outcome	ICD-9 Code	
Arterial	Ischemic Stroke (based on Protocol Core recommendation)	433.x1	Occlusion and stenosis of precerebral arteries with cerebral infarction
		434.x	Occlusion of cerebral arteries
		436	Acute, but ill-defined, cerebrovascular disease
	Myocardial infarction (algorithm used in MS AMI chart validation protocol, except they restricted to primary position inpatient diagnoses)	410.x0	Acute myocardial infarction, episode of care unspecified
		410.x1	Acute myocardial infarction, initial episode of care
Venous	Pulmonary embolism	415.1x	Pulmonary embolism and infarction
	Deep vein thrombosis (based on Protocol Core recommendation for venous thromboembolism, plus cerebral venous thrombosis and minus the 453 code series for upper extremity thrombosis)	451.11	Phlebitis and thrombophlebitis of femoral vein
		451.19	Phlebitis and thrombophlebitis of deep veins of lower extremities, other
		451.2	Phlebitis and thrombophlebitis of lower extremities, unspecified
		451.9	Phlebitis and thrombophlebitis of unspecified site
		453.1	Thrombophlebitis migrans
		453.2	Other venous embolism and thrombosis of inferior vena cava
		453.40	Acute venous embolism and thrombosis of unspecified deep vessels of lower extremity
		453.41	Acute venous embolism and thrombosis of deep vessels of proximal lower extremity
		453.42	Acute venous embolism and thrombosis of deep vessels of distal lower extremity
		453.9	Acute venous embolism and thrombosis of unspecified site
		325.xx	Phlebitis and thrombophlebitis of intracranial venous sinuses
		437.6	Nonpyogenic thrombosis of intracranial venous sinus

D. APPENDIX D: CODES USED TO SELECT THROMBOEMBOLIC EVENT RISK FACTORS

1. List of potential confounders

Below are tables displaying the details for the potential confounders (non-medication) we considered for this study. Table D 1 includes covariates not defined by specific codes. Table D 2 includes the category, condition, look back time, code type, and codes related to each potential confounder. Only a few confounders (those that are time-varying) will be considered in the primary self-controlled analyses. Most of the confounders will be used for the cohort analyses or as stratification variables in the secondary self-controlled analyses.

Table D 1. Demographic, Calendar Time, and Medical Utilization Risk Factors

Covariate	Time to define
Age (centered at age 45; linear and quadratic terms)	At baseline
Sex	At baseline
Calendar year (centered at 2009)	At baseline
Hospitalization	In last 183 days
Non-acute institutional stay (e.g., skilled nursing facility or rehabilitation facility stay)	In last 183 days
Emergency department visit	In last 183 days

Table D 2. Codes Used to Select TEE Medical Condition Risk Factors

Covariate*	Lookback period for condition (days)	Code type†	Codes
Angina or chronic ischemic heart disease	183	DX09	413.x, 414.x
Atrial fibrillation or flutter	183	DX09	427.3x
Cardiac arrhythmia other than atrial fibrillation	183	DX09	426.10, 426.11, 426.13, 426.2, 426.3, 426.4, 426.50, 426.51, 426.52, 426.53, 426.6, 426.7, 426.8x, 427.0, 427.2, 427.60, 427.9, 785.0
Central venous catheter	183	PX09	38.97
		PXC4	36555-36558, 36560-36561, 36563, 36565-36566, 36568-36571, 36575-36576, 36578, 36580-36585, 36597-36598
Cerebrovascular hemorrhage	183	DX09	430.x, 431.x, 432.x
CHF or cardiomyopathy	183	DX09	402.01, 402.11, 402.91, 425.x, 428.x, 429.3
Chronic inflammatory	183	DX09	446.x, 555.x, 556.x, 581.x, 695.4, 701.0, 710.0, 710.1, 710.2, 710.3, 710.4, 710.8, 710.9, 711.2, 714.x, 725.x

Covariate*	Lookback period for condition (days)	Code type†	Codes
condition			
Chronic renal disease	183	DX09	582.x, 583.x, 585.x, 586, 588.x, 792.5, V42.0, V45.1x, V56.0, V56.1, V56.2, V56.3x, V56.8
Coagulation defects	183	DX09	286.x, 287.x
Cognitive disorder	183 for dementia; 30 for delirium	DX09	290.3, 290.x, 291.0, 292.81, 293.0, 293.1, 294.1, 294.2x, 331.0, 331.1x, 331.2, 331.82
Complicated hypertension	183	DX09	402.x, 403.x, 404.x, 405.x
COPD	183	DX09	491.x, 492.x, 496.x
Coronary revascularization	183	DX09	996.03, V45.81, V45.82
		PX09	00.66, 36.0x, 36.1x, 36.2x, 37.22, 37.23, 88.5x
		PXC4	33510-33514, 33516-33523, 33525, 92973-92974, 92977, 92980-92982, 92984, 92987, 92995-92996
		PXHC	G0290, G0291, S2205, S2206, S2207, S2208, S2209
Diabetes without chronic complication	183	DX09	250.0x, 250.1x, 250.2x, 250.3x, 250.8x, 250.9x
Diabetes with chronic complication	183	DX09	250.4x, 250.5x, 250.6x, 250.7x, 357.2x, 362.0x, 366.41
High risk cancer	90	DX09	151.x, 157.x, 162.x, 179.x, 180.x, 181.x, 182.x, 183.x, 184.x, 186.x, 188.x, 196.x, 197.x, 198.x, 199.x, 201.x, 202.x, 203.x, 204.x, 205.x, 206.x, 207.x, 208.x, 273.0, 273.3
Hyperlipidemia	183	DX09	272.0, 272.1, 272.2, 272.3
Immobility condition	30 for burn injuries; 90 for fractures; 183 for all others	DX09	260.x, 261.x, 262.x, 263.x, 284.8x, 284.9, 288.0, 289.9, 332.0, 332.1, 334.1, 342.x, 343.x, 344.x, 707.x, 741.x, 783.0, 783.2x, 783.3x, 783.4x, 799.4, 800.x, 801.x, 802.x, 803.x, 804.x, 805.x, 806.x, 807.x, 808.x, 809.x, 820.x, 821.x, 822.x, 823.x, 824.x, 825.x, 826.x, 827.x, 828.x, 829.x, 851.x, 852.x, 853.x, 854.x, 861.x, 862.x, 863.x, 864.x, 865.x, 866.x, 867.x, 868.x, 869.x, 870.x, 890.x, 891.x, 892.x, 893.x, 894.x, 895.x, 896.x, 897.x, 925.x, 926.x, 927.x, 929.x, 948.1, 948.2, 948.3, 948.4, 948.5, 948.6, 948.7, 948.8, 948.9, 952.x, 978.x, V54.13, V54.14, V54.15, V54.16, V54.17, V54.23, V54.24, V54.25, V54.26, V54.27
		PX09	41.0x

Covariate*	Lookback period for condition (days)	Code type†	Codes
		PXHC	A4310, A4311, A4312, A4313, A4314, A4315, A4316, A4320, A4321, A4322, A4326, A4327, A4328, A4331, A4332, A4333, A4334, A4338, A4340, A4344, A4346, A4347, A4348, A4349, A4354, A4355, A4357, A4358, B4027, B4028, B4034, B4035, B4036, B4083, B4086, B4087, B4088, B4100, B4102, B4103, B4104, B4149, B4150, B4152, B4153, B4154, B4155, B4157, B4158, B4159, B4160, B4161, B4162, B4164, B4168, B4172, B4176, B4178, B4180, B4185, B4189, B4193, B4197, B4199, B4216, B4220, B4222, B4224, B5000, B5100, B5200, B9000, B9002, B9004, B9006, B9998, B9999, E0100, E0105, E0130, E0135, E0140, E0141, E0143, E0144, E0147, E0148, E0149, E0153, E0154, E0155, E0156, E0157, E0158, E0159, E0163, E0165, E0167, E0168, E0170, E0171, E0172, E0175, E0240, E0241, E0242, E0243, E0244, E0245, E0246, E0247, E0248, E0250, E0251, E0255, E0256, E0260, E0261, E0265, E0266, E0270, E0271, E0272, E0273, E0274, E0275, E0276, E0277, E0280, E0290, E0291, E0292, E0293, E0294, E0295, E0296, E0297, E0301, E0302, E0303, E0304, E0305, E0310, E0315, E0316, E0325, E0326, E0370, E0371, E0372, E0373, E0424, E0425, E0430, E0431, E0433, E0434, E0435, E0439, E0440, E0441, E0442, E0443, E0444, E0621, E0625, E0627, E0628, E0629, E0630, E0635, E0636, E0637, E0638, E0639, E0640, E0641, E0642, E0700, E0705, E0710, E0791, E0950, E0951, E0952, E0955, E0956, E0957, E0958, E0959, E0960, E0961, E0966, E0967, E0968, E0969, E0970, E0971, E0973, E0974, E0978, E0980, E0981, E0982, E0983, E0984, E0985, E0986, E0988, E0990, E0992, E0994, E0995, E1002, E1003, E1004, E1005, E1006, E1007, E1008, E1009, E1010, E1011, E1014, E1015, E1016, E1017, E1018, E1020, E1028, E1029, E1030, E1031, E1035, E1038, E1039, E1050, E1060, E1070, E1083, E1084, E1085, E1086, E1087, E1088, E1089, E1090, E1092, E1093, E1100, E1110, E1129, E1130, E1140, E1150, E1160, E1161, E1170, E1171, E1172, E1180, E1190, E1195, E1200, E1220, E1221, E1222, E1223, E1224, E1225, E1226, E1227, E1228, E1230, E1231, E1232, E1233, E1234, E1235, E1236, E1237, E1238, E1239, E1240, E1250, E1260, E1270, E1280, E1285, E1290, E1295, E1296, E1297, E1298,

Covariate*	Lookback period for condition (days)	Code type†	Codes
			E1390, E1391, E1392, E1405, E1406, E2201, E2202, E2203, E2204, E2205, E2206, E2207, E2208, E2209, E2210, E2211, E2212, E2213, E2214, E2215, E2216, E2217, E2218, E2219, E2220, E2221, E2222, E2223, E2224, E2225, E2226, E2300, E2301, E2310, E2311, E2312, E2313, E2321, E2322, E2323, E2324, E2325, E2326, E2327, E2328, E2329, E2330, E2331, E2340, E2341, E2342, E2343, E2351, E2358, E2359, E2360, E2361, E2362, E2363, E2364, E2365, E2366, E2367, E2368, E2369, E2370, E2371, E2372, E2373, E2374, E2375, E2376, E2377, E2378, E2381, E2382, E2383, E2384, E2385, E2386, E2387, E2388, E2389, E2390, E2391, E2392, E2393, E2394, E2395, E2396, E2397, E2399, E2402, E2601, E2602, E2603, E2604, E2605, E2606, E2607, E2608, E2609, E2610, E2611, E2612, E2613, E2614, E2615, E2616, E2617, E2618, E2619, E2620, E2621, G0270, G0271
Intermediate coronary syndrome or unstable angina	183	DX09	411.1, 411.8x
Ischemic stroke or central venous thrombosis	183	DX09	325.x, 433.01, 433.11, 433.21, 433.31, 433.81, 433.91, 434.x, 436, 437.6
Low risk cancer or cancer treatment	90	DX09	140.x, 141.x, 142.x, 143.x, 144.x, 145.x, 146.x, 147.x, 148.x, 149.x, 150.x, 152.x, 153.x, 154.x, 155.x, 156.x, 158.x, 159.x, 160.x, 161.x, 163.x, 164.x, 165.x, 170.x, 171.x, 174.x, 175.x, 176.x, 185.x, 187.x, 189.x, 190.x, 191.x, 192.x, 193.x, 194.x, 195.x, 200.x, V58.0, V66.1, V67.1
		PX09	92.20, 92.21, 92.22, 92.23, 92.24, 92.25, 92.26, 92.27, 92.28, 92.29
		PXC4	77371-77373, 77401-77525, 77761-77799
		PXRE	0330, 0333
Moderate to severe liver disease	183	DX09	456.0, 456.1, 456.2, 572.2, 572.3, 572.4, 572.8
Mood disorder	183	DX09	296.0x, 296.1x, 296.2, 296.3, 296.4x, 296.5x, 296.6x, 296.7, 296.80, 296.81, 296.82, 296.89, 300.4, 309.x, 311
Myocardial infarction	183	DX09	410.x, 411.0, 412

Covariate*	Lookback period for condition (days)	Code type†	Codes
Venous thromboembolism not included in outcome definition	183	DX09	336.1, 362.3x, 449, 451.0, 451.8x, 452, 453.0, 453.3, 453.5x, 453.6x, 453.7x, 453.8x, 573.4, 593.81
Other cardiovascular disease	183	DX09	420.x, 421.x, 422.x, 423.x, 429.x, 440.x, 444.x, 445.x, 745.x, 746.x, 747.x, V45.00, V45.09, V53.3x
		PXC4	33924, 75573
Other infection	183 for HIV/AIDS; 60 for all others	DX09	001.x, 002.x, 003.0, 003.20, 003.21, 003.22, 003.23, 003.24, 003.29, 003.8, 003.9, 004.x, 005.x, 006.x, 007.x, 008.x, 009.x, 020.3, 020.4, 020.5, 021.1, 021.2, 022.1, 022.2, 026.1, 031.0, 032.84, 036.0, 036.1, 036.82, 039.1, 042.x, 046.2, 047.x, 049.0, 049.1, 049.8, 049.9, 052.0, 052.1, 053.0, 054.3, 054.72, 055.0, 055.1, 056.01, 056.71, 058.2, 062.x, 063.x, 064.x, 066.2, 072.1, 072.2, 073.0, 083.0, 091.81, 094.81, 098.82, 100.81, 112.4, 112.83, 114.0, 114.2, 114.4, 114.5, 115.01, 115.05, 115.11, 115.15, 115.91, 115.95, 130.0, 130.4, 136.3, 139.0, 320.x, 321.x, 322.x, 323.x, 341.2, 480.x, 481.x, 482.x, 483.x, 484.x, 485.x, 486.x, 487.x, 488.x, 513.0, 517.1, 590.x, 595.x, 597.x, 598.0, 599.0, 711.x, 730.x
Other ischemic cerebrovascular disease	183	DX09	362.34, 433.00, 433.10, 433.20, 433.30, 433.80, 433.90, 435.x, 437.0, 437.1, 437.9, 438.x, 781.4, 784.3, 997.0
		PX09	00.61, 00.63, 38.11, 38.11, 38.12, 38.12, 38.41, 38.42, 39.28
		PXC4	0075T, 0076T, 35301, 35390, 35501, 35601, 35901, 37215-37216
		PXHC	S2211
Other venous catheterization	183	PX09	38.93
Overweight condition	183	DX09	277.7, 278.0x
Peripheral venous thromboembolism per study definition, including pulmonary embolism	183	DX09	415.1x, 416.2, 451.11, 451.19, 451.2, 451.9, 453.1, 453.2, 453.40, 453.41, 453.42, 453.9
Peripheral vascular disease	183	DX09	440.x, 441.2, 441.4, 441.7, 441.9, 443.1, 443.2, 443.8, 443.9, 447.1, 557.1, 557.9, V43.4
		PX09	38.18, 39.25, 39.29, 84.10, 84.11, 84.12, 84.13,

Covariate*	Lookback period for condition (days)	Code type†	Codes
			84.14, 84.15, 84.16, 84.17
		PXC4	27295, 27590-27592, 27598, 27880-27882, 27888-27889, 28800, 28805, 28810, 28820, 28825, 35351, 35355, 35361, 35363, 35371-35372, 35454, 35456, 35459, 35470, 35473-35474, 35482-35483, 35492-35493, 35495, 35521, 35533, 35541, 35546, 35548-35549, 35551, 35556, 35558, 35563, 35565-35566, 35570-35571, 35681-35683, 35879, 37207-37208, 37220-37235
Psychotic disorder	183	DX09	293.81, 293.82, 295.x, 297.x, 298.x
Pulmonary congestion or hypostasis	183	DX09	514.x
Sepsis and related	60 for sepsis; 183 for shock	DX09	003.1, 020.2, 022.3, 036.2, 038.x, 054.5, 449, 785.52, 785.5x, 790.7, 995.91, 995.92
Substance abuse	183	DX09	291.0, 291.1, 291.2, 291.3, 291.5, 291.8x, 291.9, 303.9x, 304.0x, 304.1x, 304.2x, 304.3x, 304.4x, 304.5x, 304.6x, 304.7x, 304.8x, 304.9x, 305.0x, 305.2x, 305.3x, 305.4x, 305.5x, 305.6, 305.7, 305.8x, 305.9x, 571.0, 571.1, 571.2, 571.3, V11.3, V65.42
Surgery	90	DX09	V67.0x
		PX09	00.7x, 00.8x, 03.4, 03.5x, 03.9x, 79.85, 79.86, 80.45, 80.46, 80.6, 80.85, 80.86, 80.95, 80.96, 81.40, 81.42, 81.43, 81.51, 81.52, 81.53, 81.54, 81.55, 84.16, 84.18
		PXC4	01214-01215, 01402, 20930-20938, 22010-22015, 22100-22116, 22206-22226, 22318-22328, 22532-22534, 22548-22585, 22590-22632, 22800-22819, 22830, 22840-22865, 27075-27079, 27130-27138, 27218, 27226-27228, 27253, 27258-27259, 27299, 27447, 27486-27487, 29861-29863, 43644-43645, 43800-43881, 49570-49575, 50010-50045, 50070, 50100-50135, 50205-50290, 50320-50340, 50370, 50382-50384, 50400-50540, 50593, 50600-50630, 50650-50660, 50700-50940, 51020-51040, 51080, 53000-53085, 53210-53275, 53400-53520, 53855, 56620-56740, 56800-56810, 57000-57335, 57530-57556, 57720, 58140-58146, 58150-58294, 58400-58540, 58600-58615, 58700-58720, 58750-58770, 58820-58825, 58920-58960, 58999, 61320-61321,

Covariate*	Lookback period for condition (days)	Code type†	Codes
			61546, 61680-61692, 61697-61710, 62160-62165, 63001-63017, 63045-63051, 63055-63066, 63075-63091, 63101-63103, 63170-63200, 63250-63295, 63300-63308, 63650-63688
		PXHC	S2083, S2213
Tobacco use	183	DX09	305.1, 649.0x, 989.84, V15.82
		PXC1	83887, 99406, 99407
		PXC2	1034F, 1035F, 4000F, 4001F, 4004F
		PXHC	C9801, C9802, G0375, G0376, G0436, G0437, G8093, G8094, G8402, G8403, G8453, G8454, G8455, G8456, G8688, G9016, S4990, S4991, S4995, S9075, S9453
Uncomplicated hypertension	183	DX09	401.x
		PXC2	4050F
Valvular disease	183	DX09	093.2x, 394.x, 395.x, 396.x, 397.x, 424.x, 746.3, 746.4, 746.5, 746.6, V42.2, V43.3
Other venous thromboembolism risk indicators	30 for HIT or trans-fusion; 90 for secondary hyper-coag-ulable state or VTE risk NOS; 183 for others	DX09	238.4, 270.4, 282.6, 289.0, 289.6, 289.81, 289.82, 289.84, 454.x, V12.51, V58.2
		PXC2	3551F, 3552F, 4044F
		PXC4	85300-85306, 85380, 85400-85421, 86147
		PXHC	P9010, P9011, P9012, P9016, P9017, P9019, P9020, P9021, P9022, P9023, P9031, P9032, P9033, P9034, P9035, P9036, P9037, P9038, P9039, P9040, P9051, P9052, P9053, P9054, P9055, P9056, P9057, P9058, P9059, P9060
		PXRE	0380, 0381, 0382, 0383, 0384, 0385, 0386, 0387, 0389, 0391

*Condition categories may be altered as we proceed with disease risk score calculations.
† Code type abbreviations: DX09 = ICD-9-CM diagnosis code, PXC4 = Current Procedural Terminology 4 (CPT-4) procedure code, PXHC = Healthcare Common Procedure Coding System (HCPCS) code

2. List of medication covariates

Below is a table displaying the drug classes to serve as covariates (medication) for disease risk score calculations.

Table D 3 includes the classes, subclass1, and subclass2 (if applicable) associated with the medications we will be considering via NDC codes, as well as HCPCS and CPT codes for cancer chemotherapy.

Table D 3. Classes and Subclasses of Medication Covariates*

Class	Subclass
Cardiovascular	Oral anticoagulants
	Antiplatelet agents (including aspirin)
	Antihypertensives
	Lipid lowering agents
	Antiarrhythmic agents
	Anti-anginal agents
Hematologic growth factors	Hematopoietic agents
Antidiabetic agents	Oral antidiabetic agents
	Insulin
Pain medications	NSAIDs and Cox-2 Inhibitors Opiates
Central nervous system	SSRI/SNRI/Tertiary amine TCA
	Antipsychotics
Hormones, steroids, or related	Corticosteroids
	Sex steroids
Cancer treatments	Thalidomide analogues (infusion chemotherapy and radiation therapy assessed using procedure codes)

*Use defined as a prescription fill during the 183-day lookback period.

3. Pregnancy and the post-partum period

Below is a table displaying the codes drawn from the Mini-Sentinel Gardasil Study to identify pregnancy and the post-partum period for excluding pregnant patients from the exploratory cohort analyses (pregnant patients will be excluded based on chart review in the self-controlled analysis). Table D 4 lists codes indicative of pregnancy or post-partum status and time frames from an encounter with that code during which an individual will be classified as pregnant or post-partum. These classifications will require scanning of records after the risk and control intervals, as many indicate that an individual was pregnant or post-partum prior to the encounter in which a pregnancy-related code is observed.

Table D 4. MS IVIG-TEE Codes for Identification of Pregnancy and the Post-partum Period

Category*	ICD-9 Code	Description	Period considered pregnancy or post-partum relative to diagnosis date	First-in-X-days criterion
Stillborn	656.4	Intrauterine death affecting management of mother	–42–280	280
Stillborn	656.4	Intrauterine death	–42–280	280

Category*	ICD-9 Code	Description	Period considered pregnancy or post-partum relative to diagnosis date	First-in-X-days criterion
		affecting management of mother unspecified as to episode of care		
Stillborn	656.41	Intrauterine death affecting management of mother delivered	–42–280	280
Stillborn	656.43	Intrauterine death affecting management of mother antepartum	–42–280	280
Stillborn	768	Fetal death from asphyxia or anoxia before onset of labor or at unspecified time	–42–280	280
Stillborn	768.1	Fetal death from asphyxia or anoxia during labor	–42–280	280
Stillborn	V27.1	Mother with single stillborn	–42–280	280
Stillborn	V27.3	Mother with twins one liveborn and one stillborn	–42–280	280
Stillborn	V27.4	Mother with twins both stillborn	–42–280	280
Stillborn	V27.6	Mother with other multiple birth some liveborn	–42–280	280
Stillborn	V27.7	Mother with other multiple birth all stillborn	–42–280	280
Stillborn	V32*	Twin birth mate stillborn	–42–280	280
Stillborn	V35*	Other multiple birth (three or more) mates all stillborn	–42–280	280
Stillborn	V36*	Other multiple birth (three or more) mates liveborn and stillborn	–42–280	280
Preterm	644.2*	Early onset of delivery delivered with or without antepartum condition	–42–258	280
Delivery	650*	Normal delivery	–42–280	280

Category*	ICD-9 Code	Description	Period considered pregnancy or post-partum relative to diagnosis date	First-in-X-days criterion
Delivery	669.5*	Forceps or vacuum extractor delivery without mention of indication	–42–280	280
Delivery	669.6*	Breech extraction without mention of indication	–42–280	280
Delivery	669.7*	Cesarean delivery without mention of indication	–42–280	280
Delivery	V24*	Postpartum care and examination	–42–280	280
Delivery	V27.0	Mother with single liveborn	–42–280	280
Delivery	V27.2	Mother with twins both liveborn	–42–280	280
Delivery	V27.5	Mother with other multiple birth all liveborn	–42–280	280
Delivery	V27.9	Mother with unspecified outcome of delivery	–42–280	280
Delivery	V30*	Single liveborn	–42–280	280
Delivery	V31*	Twin birth mate liveborn	–42–280	280
Delivery	V33*	Twin birth unspecified whether mate liveborn or stillborn	–42–280	280
Delivery	V34*	Other multiple birth (three or more) mates all liveborn	–42–280	280
Delivery	V37*	Other multiple birth (three or more) unspecified whether mates liveborn or stillborn	–42–280	280
Delivery	V39*	Liveborn unspecified whether single twin or multiple	–42–280	280
SAB	632*	Missed abortion	0-105	280
SAB	634*	Spontaneous abortion	0-105	280
TAB	635*	Legally induced abortion	0-105	280
TAB	636*	Illegal abortion	0-105	280

Category*	ICD-9 Code	Description	Period considered pregnancy or post-partum relative to diagnosis date	First-in-X-days criterion
TAB	637*	Unspecified abortion	0-105	280
TAB	640.01	Threatened abortion delivered	0-105	280
TAB	640.81	Other specified hemorrhage in early pregnancy delivered	0-105	280
TAB	640.91	Unspecified hemorrhage in early pregnancy delivered	0-105	280

*SAB = spontaneous abortion; TAB = therapeutic or elective abortion

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