Plasma Protein Therapeutics Association

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VIA EMAIL
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Mini-Sentinel Operations Center

SUBJECT: Project Title: Posted for Public Comment until October 4, 2013: Thromboembolic Events After Immunoglobulin Administration Protocol ("Protocol")

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Dear Mini-Sentinel:

The Plasma Protein Therapeutics Association (PPTA) thanks Mini-Sentinel for the opportunity to participate in the protocol review process and is pleased to provide our comments on the Thromboembolic Events After Immunoglobulin Administration Protocol. PPTA is the international trade association and standards-setting organization for the world's major collectors of Source Plasma and manufacturers of plasma-derived products and recombinant analogues, collectively referred to as plasma protein therapies, which are used in the treatment of a number of rare diseases. These diseases are often genetic, chronic, life-threatening conditions that require patients to receive regular infusions or injections of plasma protein therapies for the duration of their lives. Plasma protein therapies include clotting-factor therapies for individuals with hemophilia A and B and other bleeding disorders; immunoglobulins to treat a complex of diseases in individuals with immune deficiencies; therapies for individuals who have alpha-1 anti-trypsin deficiency, which typically manifests as adult onset emphysema and limits substantially life expectancy; and albumin, which is used in emergency-room settings to treat individuals with shock, trauma, burns, and other conditions. PPTA members are committed to ensuring the safety and availability of these medically needed, life-sustaining therapies.

General Comments

While PPTA appreciates the opportunity to participate in protocol **review**, the Association would like to reiterate the point, most recently made at the FDA/PPTA Liaison Meeting on September 20, 2013, that industry engagement during protocol **development** will help Mini-Sentinel create more robust protocols. PPTA continues to request FDA feedback on ways to increase industry participation in the *Mini-Sentinel* pilot and, eventually, the *Sentinel Initiative*. Recognizing that

this Protocol is the first in Blood-SCAN, PPTA echoes its offer made at the Liaison Meeting to cooperate in protocols on other plasma protein therapeutics (such as hyperimmune globulins), outcomes, and product-outcome pairs.

PPTA also would like to reiterate its previous comments to FDA, including most recently at the September 20 Liaison Meeting, that Agency data on immune globulins (Ig) and thromboembolic events (TEE) (Reference 28) lack validation and are subject to residual confounding. FDA asserted at the Liaison Meeting that the Protocol mitigates such confounding with a self-controlled method using exposure time and non-exposure time. While PPTA appreciates FDA's efforts to address the Association's data validation concerns, the Association notes that the self-controlled method is not a validation method; rather it is intended, as indicated in the Protocol, to control for TEE risk factors. Given the well-recognized uncertainties associated with medical billing codes, only a full case work up for all individuals in the analysis will be able to ascertain how accurate the billing data are for determining incidents of TEE. Moreover, even if the self-controlled method does in some way address PPTA's data validation concerns, the Association also notes that the method is used in only part of the Protocol and remains concerned that the results of the Protocol will lack validation for this and other reasons.

Importance of Chart Review

PPTA would like to stress the importance of chart review and verification, without which data are not considered validated, and to express concern regarding this language in the Methods section (pp. 14-15):

> It would be preferred if all arterial TEE cases identified in the MSDD that occur in the risk or control windows following an Ig dose could undergo medical record review. However, preliminary modular program requests (Table 2) identified more exposed cases than can feasibly and cost-effectively be chart-reviewed. In addition, 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 [sic] 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 – no more than several dozen patients per Data Partner.* (emphasis added).

Chart confirmation should be done for all cases identified in the analysis. As many in industry invest thousands of hours every year tracking down details about AERs and assessing their significance, PPTA recognizes that retrospective chart review is a difficult, time-intensive process, even in safety databases. This difficulty is enhanced further in *Mini-Sentinel* by the fact that the databases are composed of administrative claims, not safety reports. With the inaccuracies inherent in a claims-based database it is imperative to validate the case definitions and not depend on billing codes used in the search algorithm. Also lacking in the Protocol is any discussion of presenting data on the accuracy of the case detection searches and whether they differ among the various partners supplying data for this crucial analysis. Misclassification of cases can severely bias the analyses. PPTA believes that confirmatory chart review can be carried out for all patients in this study, particularly in light of the low number of TEE cases seen in industry pharmacovigilance, and questions the rationale for not doing so. While it is indicated

that the "preliminary modular program requests (Table 2) identified more exposed cases than can be feasibly and cost-effectively be chart reviewed," the numbers in the Table appear quite low: 131 potential arterial events and 179 potential venous events. In addition, are not all these cases included in the power calculation analysis (p. 17)? Of key importance in these analyses is the evaluation of patient risk factors that could promote TEE and it is important to ensure the sample size is adequate and well-documented.

PPTA also would like to express concern regarding prioritization of charts for review as reflected in this language earlier in the Methods section (p. 10):

> It is possible that the number of potential cases may exceed the available budget for chart review. *Charts will be ranked in order of priority for review, with priority determined according to several factors based on the results of the first Work Plan*. For example, potential cases with inpatient diagnoses in primary and nonsecondary positions will be prioritized over inpatient diagnoses in secondary positions and emergency department diagnoses; IVIg use with a documented indication in the electronic data will be prioritized over IVg [sic] with no indication documented; and other factors will be considered that are also likely to be good predictors of a higher PPV. (emphasis added).

What are the other a priori factors that will be considered as likely good predictors of a higher positive predictive value (PPV)? Where do they fall in the rank ordering of priority for review? A list of these factors that the Authors have identified is important since they will be used for case ascertainment. PPTA notes the lack of detail regarding how potential cases will be adjudicated for priority, i.e. how patients will be chosen. A chart-confirmed data set, appropriately redacted for patient identifiers and other personal information, should be shared with subject matter experts for adjudication. PPTA also notes that many indications for Ig exist, both on- and off-label. As such, PPTA respectfully requests that the Authors clarify, and Mini-Sentinel post for public comment, the scheme by which charts will be prioritized, whether as part of the Work Plan or otherwise.

Need to Focus on Patient Risk Factors

Although it is extensively reported that underlying patient condition is a major contributor to the risk of TEE, the following Objectives are not Primary or Secondary Objectives but instead Exploratory Objectives Based on Chart Confirmed Data: "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)" (Objectives section, pp. 4-5). Data on potential, underlying/pre-existing risk factors and relative importance between risk factors are very valuable and of central importance, particularly for certain patient populations and for clinicians. In fact, patient risk factors may be the most informative of all possible outcomes and should be more of a priority and a significant component of the Protocol, i.e. a Primary or Secondary Objective. This is particularly relevant since the data set covers a large time interval and it is only with sufficient numbers of cases that an assessment of patient risk factors can be made. Identification of differences in various Ig products used in this time period PPTA feels has limited usefulness since small sample sizes will have limited ability to discriminate between products and as indicated there have been product modifications since the one-time increased incident of adverse events was detected.

Additional Comments Organized in Table Format

Section	*Page(s)*	*Comment*
I. BACKGROUND	1	The Background states that "FDA-approved products are listed in Table 1. There are 13 different products." However, this is not an exhaustive list. For example, GamaSTAN S/D is singled out as the only IM product approved by FDA without further elaboration. This is clearly not the case. If it is the only product of its class included in the study, data obtained would not be interpretable without a valid comparator. None of the RhoD Ig products (IM or IV) are included, without comment or justification, despite their long-term use history. Other Ig products that could be considered include: • Cytomegalovirus Immune Globulin Intravenous (Human) • Three Hepatitis B Immune Globulins (Human) and one Hepatitis B Immune Globulin Intravenous (Human) • Two Rabies Immune Globulins (Human) • Two Rho(D) Immune Globulins (Human) and two Rho(D) Immune Globulins Intravenous (Human) • One each of Tetanus, Vaccinia and Varicella Zoster Immune Globulins (Human)
V. APPENDICES B. APPENDIX B: LIST OF IMMUNOGLOBULIN EXPOSURE CODES	32	At the same time, Appendix B states: 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. (emphasis added). PPTA seeks to clarify that Table B 1. MS IVIG-TEE Codes for Ig Administration (excluding NDCs), not Table 1, reflects the Ig products to be studied. The selection of products to be included/excluded should be discussed and justified. PPTA suggests either including all IMIg products or excluding all. In any event, all IVIg products should be included. In addition, PPTA would like to express concern that the "codes will be further evaluated prior to implementation." Which Ig products will be studied is an important factor in the Protocol for many reasons, including comparators as expressed, and should not be changed outside of the review process. PPTA also would like to express concern that the Authors "may restrict exposure codes … to identify IVIg use for chart review, and further restrict to Ig users *with plausible indications through associated diagnosis codes in claims data*" (emphasis added). What criteria will be used for determining "plausible indications" given the variety of conditions for which Ig has been used to treat? It also appears that this statement is not in synchronization with the earlier statement that the Authors "will identify health plan members of any age with administration of any product (IV, SC, or IM) … " (p. 9). PPTA respectfully requests that the Authors clarify these two statements.
I. BACKGROUND	1	PPTA questions the validity of the statement "[t]he majority of patients have only one Ig treatment episode … ."
I. BACKGROUND II. OBJECTIVES C. EXPLORATORY OBJECTIVES BASED ON CHART CONFIRMED DATA	2 5	"In response to this issue, manufacturers of Ig products instituted their own testing and *modified manufacturing processes to reduce Factor XIa leve*ls." (emphasis added) "Recency of product: whether Ig product was delivered (and presumably manufactured) in 2011/2012 *after efforts were undertaken to reduce risk of TEE*." (emphasis added) These statements reflect a basic misunderstanding

		of the products being studied; the References cited (21, 23, 24) do not support these assertions. PPTA understands that, with the exception of a single, well-documented case, no changes in manufacturing methods or controls have been implemented for any product during the study period. In addition it is highly unlikely that with the short time period since any manufacturing changes that a comparison can be made to detect changes in TEE incidence.
I. BACKGROUND	3	PPTA first learned of the Blood-SCAN Feasibility Evaluation in this language: > Information from the previous Blood-SCAN Feasibility Evaluation has informed the design of this protocol based assessment. The Feasibility Evaluation identified 185 TEE (narrow definition) within 14 days of Ig use during 2006-2012 among 32,112 unique IVIg users. 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. (citation omitted) (emphasis added). PPTA is concerned that the Authors based the design of the Protocol on a feasibility evaluation that is dated over one year ago (August 10, 2012) and has yet (as far as PPTA can tell) to be published or shared with industry. It appears, in fact, that "modular program feasibility analyses" followed the initial feasibility evaluation and also informed the design of the Protocol. PPTA respectfully requests

		that Mini-Sentinel publish and/or provide copies of the evaluation and analyses to PPTA.
II. OBJECTIVES B. SECONDARY OBJECTIVES	4	PPTA would like to express concern regarding the Secondary Objective, "For each primary objective, explore whether the relative risk is modified by Product/brand" and questions the value of this Objective given the low raw number of cases of TEEs. PPTA suggests that the Authors move the "Product/brand" analysis to the Exploratory Outcomes Based on Administrative Data with the following rationale: • In Appendix B, there are several entries coded as product "unspecified" • The quality of data in these claims data is unknown but expected to be inadequate for good adjudication of cases • Many risk factors exist in the data set, which would be difficult to control for without a meaningful number of cases for each factor (age, underlying conditions, concomitant medications, etc.) • The distribution channel and the target patient demographics are different for the various products and are not controlled in this study • Based on these reasons, "Product/brand" relative risk assessments can be considered exploratory at best
IV.POWER CALCULATION	17	In particular, the Power Calculation does not sufficiently describe a statistical method for making a relative risk determination but only describes the power to detect/predict a relative risk of 1.65 (80%); the power depends on the number in each group, which will be small. While there may be value as an academic exercise, PPTA cautions that if the results include relative risk by "Product/brand," there also is pragmatic potential to affect patient access. In fact, in an FDA/HealthCore poster presented on August 28, 2013, at the 29th ICPE in Montreal, Occurrence of Hemolytic Reactions (HRs) on the Same Day as Immune Globulin (IG) Product Administrations during 2008-2012 (Divan et al.), FDA has already published suggestions that such an association exists based on statistically non-significant results. PPTA suggests that if the Authors intend to give relative

		risk by "Product/brand," more specific criteria should be established for making such distinctions. It should be explicitly defined how such important inferences will be drawn.
II. OBJECTIVES B. SECONDARY OBJECTIVES	4-5	The Protocol should describe the method used to stratify results per Dose or Type of Indication (primary immunodeficiency, secondary immunodeficiency, inflammatory/other).
II. OBJECTIVES C. EXPLORATORY OBJECTIVES BASED ON CHART CONFIRMED DATA III. METHODS C. POTENTIAL CONFOUNDERS H. PRIMARY ANALYSIS OF POOLED DATA AND EXPLORATORY ANALYSES OF DATA DISTRIBUTED ACROSS DATA PARTNERS	5 11 14	As noted, one of the Exploratory Objectives Based on Chart Confirmed Data will use "disease risk scores." Further details regarding the "disease risk score calculations" and "disease risk score algorithms" are provided throughout the Protocol, including this language: > They will adjust for measured TEE risk factors that might be confounders in between-person comparisons, using a *disease risk score* summarizing demographics, comorbidities and treatments identified during the 183-day baseline period. … The main purpose of these codes is two-fold, 1) to develop a *disease risk score* that will be used to stratify self-controlled cases based on level of risk, and 2) to adjust for risk factors within the exploratory cohort analyses. … 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. and this language: > For *disease risk scores,* the smaller Data Partners will use a *disease risk score* comprised of an average of the *disease risk score algorithms* from the five largest Data Partners (Humana, Aetna, Optum, HealthCore, and Kaiser Permanente). Each of the five largest partners will use the *disease risk score* based on their own data. (emphases added).

		However, PPTA respectfully requests that the Authors clarify whether these scores will be generated solely for the purpose of this study or already existing scores will be used. It also appears that at least 6 (5 large Partner scores and one average score for small health plans) disease risk scores will be employed. How are they derived and how do they differ by Data Partner?
II. OBJECTIVES D. EXPLORATORY OBJECTIVES BASED ON ADMINISTRATIVE DATA	5	There is no indication of how "overall trajectory of TEE incidence" (Items 2 and 3) will be measured. Item 2 includes differences in route of administration, but as noted, the Protocol lacks clarity regarding the Ig products to be studied so the analysis in this regard may be critically incomplete. Item 3 includes the remarkable Objective of "examining what the TEE risk would have been among the Ig-treated individuals had they never been treated with Ig." How this will be established is not clear. At best a hypothetical estimate of TEE risk in a similar, but untreated, patient population could be calculated; however, it would not represent the risk the patients "would" have had if untreated. If it is to be based on a comparison of individuals with similar indications who did not receive Ig (p. 6), the Authors should establish the equivalence of these two populations. If this is the case, the Authors also should make the Objective a Secondary Objective. As noted, it is extensively reported that underlying patient condition is a major contributor to the risk of TEE. A relative risk assessment of all individuals with indications for Ig who were treated with Ig versus those who were not should be a Secondary Objective, especially for labeled indications and other indications, if the data allow it. Item 4 is an alternative to the Primary Objective of establishing estimable risk, but in this case, presumably, based on data that are not confirmed in the charts. This undisciplined importation of what may well be lower quality data creates a risk of undermining the overall validity of the study.
III. METHODS A. DATA SOURCE AND	5-6	PPTA understands that the Protocol will analyze new users of IVIg, prevalent users of Ig, and nonusers of

STUDY POPULATION		Ig as described by this language: > *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 prevalent users as well as new users. (emphasis added). The decision to focus on "new users" and the criteria on which they will be selected deserve some discussion and medical/scientific justification. Based on the definition given and prior studies, is it this group that is expected to exhibit the highest rate of TEEs or the lowest? The selection is critical to informing clinicians in a meaningful way of how to assess treatment options for the majority of their patients.
III. METHODS C. IDENTIFICATION OF IMMUNOGLOBULIN NEW USERS	9	The Protocol describes "new Ig users" adequately, but does not provide a rationale for this selection. Contrary to the Authors' assertion that the majority of patients have only one Ig treatment episode, the majority of IVIg recipients are treated repeated, if not lifelong. While there may be technical reasons for selecting this population, it risks excluding the very population for which the results would be most informative. PPTA respectfully requests that the Authors provide a clear justification for this restriction and an analysis of how it will impact the applicability of the study results to the general population of IVIg users. PPTA also is concerned that the restriction of the primary analyses to new users of IVIg may bias the results. While using only new users of IVIg eliminates background complications, it also leads to overrepresentation of sub-sets of the Ig patient population and to possibly biased results. Although "[s]tratified Cox regression will be used for the exploratory analyses" including "all Ig-treated individuals, including IM, SC and IV, and including prevalent users as well as new users," these analyses will be minor. For example, while dose- and indication-effect will be studied in the primary analyses (only new users of IVIg), they appear to be lacking in the exploratory analyses (new and

		prevalent users of Ig). In addition, PPTA respectfully requests that the Authors provide more detail on the exploratory cohort analyses, e.g. stratified Cox regression, control variables (pp. 13-14).
III. METHODS A. DATA SOURCE AND STUDY POPULATION	6	PPTA also understands that, in addition to new users of IVIg and prevalent users of Ig, "[a]nother set of exploratory analyses will include individuals with indications for Ig treatment but who did not receive Ig treatment." PPTA respectfully requests that the Authors also provide more detail on how these individuals will be chosen and, as suggested, make the results of these analyses a Secondary Objective.
III. METHODS B. STUDY DESIGN AND ANALYSIS PLAN	8-9	Exploratory analyses related to route of administration are to be done without the benefit of chart confirmation. Since non-IV routes of administration represent a minority of expected cases, chart confirmation would not seem overly burdensome. It would also be valuable to confirm product use for an approved indication by an approved route of administration.
III. METHODS C. IDENTIFICATION OF IMMUNOGLOBULIN NEW USERS	9	PPTA understands that the Authors "will exclude individuals who initiated more than one product of interest on the index date" and that "[t]he primary analysis will be focused on the risk of TEE after Ig in all IV products combined." Since at least the intent does not appear to be to compare products, but rather show risk associated with Ig use and the impact of specific risk factors, why exclude individuals who have more than one product administered? It would be valuable from the health claims databases to also know the frequency of multiproduct administration, i.e. how common is this occurrence?
III. METHODS I. THROMBOEMBOLIC EVENTS AND IMMUNOGLOBULIN EXPOSURE VALIDATION	15	The discussion of ischemic stroke and its definition deserves medical review, especially with respect to neural deficits >24hr without imaging.
V. APPENDICES A. APPENDIX A: DEFINITIONS OF INDICATIONS FOR IMMUNOGLOBULIN USE	18-31	Some, but not all, indications for which IMIg is prescribed are included (varicella, CMV). It is unclear as to why the Protocol does not mention the majority of indications for which IMIg (and some IVIg) has been approved. PPTA respectfully requests that the

		Authors **explicitly confirm** that route of administration and indication being treated will be collected for each case in the study, which appears to be the case. PPTA also respectfully requests that the Authors explain the meaning of the frequent entry "[added subsequent to review of dx preceding IVIg administrations]."
V. APPENDICES B. APPENDIX B: LIST OF IMMUNOGLOBULIN EXPOSURE CODES	32-34	Attempts should be made to minimize "unspecified" product codes; for example, attempts should be made to get the NDC codes based on chart review to identify the product used. PPTA also respectfully requests that the Authors verify that no HCPCS codes are available for hyperimmunes especially RhoD products.
V. APPENDICES C. APPENDIX C: DIAGNOSIS CODES FOR SERIOUS THROMBOEMBOLIC EVENTS	34-35	PPTA questions whether these are the only codes that will be counted as TEE and asks the Authors to clarify. While they are indisputably serious, they are not inclusive.
V. APPENDICES D. APPENDIX D: CODES TO BE USED TO SELECT THROMBOEMBOLIC EVENT RISK FACTORS	36-50	The codes in Tables D 2, D 3, and D 4 are enormously complex and deserve medical review. As noted, underlying risk factors are pivotal to the value of this study, yet how they will be used in the analysis is inadequately described.
Not Applicable	N/A	Effects of switching products, patient compliance, and impact of hospitalization are not addressed.

Conclusion

PPTA appreciates the opportunity to comment on the Thromboembolic Events After Immunoglobulin Administration Protocol and looks forward to continued work with Mini-Sentinel during the review process. PPTA welcomes from Mini-Sentinel any questions regarding these comments. Thank you for your consideration.

Respectfully Submitted,

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