Comparative Effectiveness Research Review Disposition of Comments Report

Research Review Title: *Comparative Effectiveness of In-Hospital Use of Recombinant Factor VIIa for Off-Label Indications vs. Usual Care*

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Comments to Research Review

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Comments on draft reviews and the authors' responses to the comments will be posted publicly on the Effective Health Care Web site within three months after the final review is published. Comments are not edited for spelling, grammar, or other content errors. The table below includes the response by the authors of the review to each comment submitted for the draft review.

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Section	Comment	Response
Executive Summary	This review has 3 main specific stated aims; that is: 1. "to characterise the use of VIIa, 2. identify comparative studies and 3. review evidence for effectiveness in selected clinical settings". These clinical settings include intracranial, trauma, liver transplantation, cardiac surgery and prostatectomy.	The Report continues to emphasize these major aims.
Executive Summary	There is a major problem with the demographic description of FVIIa use. The Premier database captures only hospital use, which is largely off-label. I have queried the company on several occasions about their market in the US. The (admittedly informal) response I have gotten is that 80% of patients in the US are off-label, but 80% of doses (or sales) are on-label. This is because a single hemophiliac with inhibitors might use prodigious amounts of the drug, mostly as an outpatient, during a single episode of bleeding. I have no reason to doubt this statement -- perhaps the reviewers could get actual data from the company to clarify this point? I believe that an accurate description of use would substantially change some of the introductory and concluding material in the report.	In all relevant areas, we have highlighted that the Premier data is limited to in-hospital applications of rFVIIa. We also note that the majority of use is outpatient. However, a detailed analysis of outpatient use was not possible because of the lack of national data on patterns of use in the home setting. We appreciate that having better information about non-hospital use of rFVIIa would have been optimal.
Executive Summary	See my comments above regarding key messages. Of course there have been more studies published or presented since this review began. In particular there is now top line data available from a 600 patient prospective randomized trauma trial. Fortunately it tends to confirm the information already presented: insufficient power to determine a mortality benefit; improvement in transfusion requirements; no increased risk of thrombosis. See my comments above about implications and omitted literature. Translation into future research is going to involve issues of informed consent that will require new methods to resolve.	We have included further information about the CONTROL trauma trial. Unfortunately, at this point in time there is no publication available on the trial itself, although some information is contained via the Novo Nordisk website and in a commentary discussing the trial's lack of success in reaching its endpoints (Dutton R, Hauser, Boffard K, et al. Scientific and logistical challenges in designing the CONTROL trial: recombinant factor VIIa in severe trauma patients with refractory bleeding. Clinical Trials, 2009; 6: 467-479).
Executive Summary	Page 19. I am not sure what "Earlier administration may increase benefit, but may be confounded with earlier CT scanning" means. It sounds like this is some kind of a drawback, but it is not. Studies simply need to control carefully for the timing of the baseline CT when investigating the hemostatic effects of rFVIIa.	We have revised our language and states, in both the Executive Summary and main report, that the analysis of earlier rFVIIa administration is difficult to interpret because of potential confounding with timing of CT scanning and that past studies may have not accounted adequately for this potential confounding (pages ES-9 and 75).
Executive Summary	Key Question 2. Are there subpopulations of patients based on demographic or clinical factors who are more likely to benefit from rFVIIa use? I would again highlight coagulopathic patients.	The report has been modified to highlight for this Key Question on intracranial hemorrhage that the subpopulation of coagulopathic patients is one that may benefit from future study because there is only one small observational study on this

		patient population, which limits applicability and conclusions (pages 76-77).
Executive Summary	Overestimation of off-label use of rFVIIa The Draft Report erroneously concludes that the use of rFVIIa outside of approved indications is now the main component of rFVIIa use and is "common" in a variety of critical bleeding settings. This conclusion is wrong for several reasons:	The report's assessment of practice patterns is limited to inpatient care and does not assess the proportion of overall use that is off-label versus on-label. We have emphasized to a greater extent that its focus is on inpatient use (see immediately below). Within the hospital setting off-label rFVIIa use is substantial.
Executive Summary	L. Patterns of Use 1.1 Overestimation of off-label use of rFVIIa A stated rationale for this review is that the majority of rFVIIa use is outside of approved indications. This is emphatically not the case. The Draft Report erroneously concludes that the use of rFVIIa outside of approved indications is now the main component of rFVIIa use, and is now common in a variety of critical bleeding settings. This conclusion is incorrect for several fundamental reasons, as will be explained. In the off-label use that does occur, it has been a consistent finding throughout the reported clinical experience that the administration of rFVIIa is frequently associated with a cessation or significant slowing of blood loss in situations where other conventional methods such as transfusion and component therapy fail. Nonetheless, we would vigorously dispute the assertion made in this document that the off-label use of rFVIIa has become "routine".	The report has been modified to remove the word "routine". We have stated that "During the past decade, however, in-hospital off-label use of rFVIIa has increased" (page ES-1).
Executive Summary	12 Inherent properties of at-risk population being analyzed. L2J Role of rFVIIa use in unmet medical needs The Executive Summary of the Draft Report states in reference to the uncertainty surrounding the data supporting off-label drug use: "In some instances, the data supporting off-label drug use falls short of the rigor that accompanies FDA review. This uncertainty may be acceptable if uses are Infrequent and in extraordinary circumstances." As the data in the Draft Report demonstrate, rFVIIa is only used in between 1% to 3% of cases, meeting the definition of infrequent use. Case studies provide support for its potential use in the context of these extraordinary circumstances. Consideration as to the "extraordinary circumstances" (defined as patients with uncontrolled life-threatening bleeding) surrounding much of the off-label use of rFVIIa is not addressed in any way in this Draft Report, with the possible exception of the acknowledgment of a 27% in-hospital death rate (page ES-6) for patients who were treated with rFVIIa. Unfortunately, given the lack of efficacy (as defined from the regulatory perspective) concluded by the analysis presented in the Draft Report, even this acknowledgment may lead some to question the role of rFVIIa in contributing to the mortality	The report notes that rFVIIa is used in situations where there may be few therapeutic options (page 31). However, there are other issues that may raise concerns, regardless of the number of therapeutic options or the (in)frequency of use. This has been clarified in the Executive Summary. The analytic framework specifically notes that rFVIIa use may occur prophylactically, as a treatment for a specific bleeding problem, and in end-stage use where other strategies have failed (page 31). Again, it is important to note that despite the common sense assumption that cessation of bleeding would lead to improved outcomes, this conclusion has not been substantiated in high quality studies. The report introduces the possibility of this discrepancy early on (page 31) and notes the findings of such a discrepancy in the discussion section—which posits that it may be related to rFVIIa's use when disease progression cannot be reversed (despite reversal of bleeding) and/or potential harms produced by the administration of rFVIIa. (page 182).

	rate. A commonsense consideration of the areas where rFVIIa is being used off-label raises the probability that this use is being driven by unmet medical needs. The common element in trauma, ICH and cardiac surgery that leads to rFVIIa use is the desire to treat life-threatening hemorrhage in patients unresponsive to standard modes of treatment. In trauma, uncontrolled bleeding leads to rapid death. In this setting, once all routine measures are utilized (e.g., clamps, plasma transfusions, tourniquets, vascular ligation and topical hemostatics), there remains no approved blood clotting agents available to employ. In this setting, the consequence of the lack of efficacy of any therapy that might be utilized is the same as the risk of doing nothing—i.e., the patient bleeds to death. If the agent is effective in aiding the V control of bleeding, the risk of a subsequent thrombotic event (if not too high) is typically deemed by the physician worth the risk if the patient survives in the short term. The unmet medical need in this setting is an approved therapy that is effective in controlling life-threatening hemorrhage due to trauma. The use of rFVIIa in ICH offers a similar scenario. Intracranial hemorrhage is associated with high mortality or profound morbidity. There is currently no proven treatment for ICH. 15 The problem is brain hemorrhage, which often continues to expand and destroy brain tissue over the first few hours after the initial bleeding. 16'8 Surgery (i.e., hematoma evacuation) has been shown to be without benefit. 19 In the setting of ICH, one of the most effective ways to ensure that a hemostatic agent targets the source of bleeding in the brain tissue is through the vasculature. Recombinant FVIIa is an intravenous hemostatic agent reported to arrest or slow ongoing hematoma expansion versus usual care. The options for the treating physician are to watch the patient die, to watch as further hemorrhage creates more neurologic damage that is typically irreversible or to try to intervene with an agent that may reduce or stop the bleeding. The unmet medical need in this setting is an approved hemostatic agent that is effective in controlling ICH in an effort to reduce morbidity and mortality. While one Phase 2 trial and one Phase 3 trial were both able to show a reduction in bleeding with the use of rFVIIa, they were not able to meet the goals of significant reductions in morbidity and mortality. A subsequent publication presents exploratory analyses in which a subset of ICH patients was described to have benefited significantly from rFVIIa treatment both in hemorrhage cessation and improved outcomes. While unproven, the risk-benefit analysis by some physicians is that any potential benefit to be gained is still worth the risk in this setting. The setting of cardiovascular surgery is somewhat different than that for trauma or ICH, but there is clearly a continuing unmet medical need. Bleeding is a problem in some cardiac cases and	

	the desire to reduce oc limit blood transfusion is uniform with all cardiac surgery. Aprotinin, an agent which was widely used to decrease bleeding and reduce the need for transfusion in cardiac surgery, has been virtually eliminated from the market (see Figures 1 and 2). This has created a significant void in the armamentarium of surgeons or anesthesiologists in their efforts to reduce bleeding during these surgeries. Although routine local methods of hemostatic control can be used, an intravenous route with an agent such as rFVIIa is potentially useful in controlling hemorrhage. Although not approved for this use, some physicians may use their discretion based on their medical experience to make the decision that the risk of thrombosis is worth the benefit of controlling hemorrhage in certain cases. Indeed, the use of rFVIIa has been cited in the evidence-based guidelines for the management of bleeding in cardiac surgery (Society of Thoracic Surgeons [STS] Guidelines). According to the STS guidelines, "the use of recombinant factor VITa concentrate is not unreasonable for the management of intractable nonsurgical bleeding that is unresponsive to routine hemostatic therapy after cardiac procedures using CPB". 3 A comprehensive multicenter review of the off-label use of rEVIIa in cardiac surgery in Canada has also found that the use of rFVIIa was associated with a highly significant reduction in the rate of administration of blood and blood products. When the cohort receiving rFVIIa was compared to a risk-adjusted population of cardiac surgical patients not receiving rFVIIa, there appeared to be neither an increase nor a decrease in the short-term complication rates. 4 The problem is uncontrolled hemorrhage (bleeding that does not stop) or excessive hemorrhage (bleeding that requires multiple units of transfusion) and the unmet medical need is an effective, approved intravenous hemostatic agent.	
Executive Summary	12.2 Possible impact of concomitant therapy on occurrence of serious adverse events. One of the conundrums faced by those who would seek to investigate therapies for massive bleeding is that many of the adverse effects seen in immediate survivors of life-threatening hemorrhage (especially thromboembolic events) may be attributed to the pro-thrombotic effect of the hemostatic agent under test. However, these adverse effects may also be attributable to the pro-thrombotic effects of the massive transfusions that invariably accompany the use of a rescue hemostatic agent. Unfortunately, this possibility and the most cogent paper addressing this relationship (reference 179 in the Draft Report23) are ignored in the Draft Report. Koch24 has similarly published that peri-operative red blood cell transfusion is the single factor most reliably associated with increased risk of postoperative	The purpose of conducting an RCT is to control for the impact of concomitant therapies, amongst other things. Both treatment and control arms of a study have an equal likelihood of exposure to concomitant therapies that may alter the effectiveness of rFVIIa.

	morbid events after isolated coronary artery bypass grafting.	
	Introduction	
Introduction	My affiliation is XXX.	We have corrected the affiliation information.
Introduction	"Even among those patients with inhibitors, desensitization protocols can yield responsiveness to factor replacement." This understates the significance of inhibitors in hemophilia A and B, by implying that desensitization is a simple matter. The cost of desensitization has been shown to cost between $900,000 and $1,600,000 in patients with hemophilia A and inhibitors, depending on the prognostic factors and age/size of patient. It also takes many months or more than a year to accomplish, so it is not as simple as desensitization to an antibiotic like penicillin, for instance. Reference to that point is Mariano G and Kroner B, Transfusion (2000) 40(4):495-496. Further, desensitization to factor IX inhibitors leads to anaphylaxis, and is not recommended.	The Report reflects that desensitization is not always a viable choice, but is relatively frequent in some centers. There appears to be regional variation in its use. The Report more clearly describes the potential role of desensitization and emphasizes that it is neither simple nor inexpensive. The Report states "Among patients with inhibitors, a fraction can be desensitized and can again become responsive to factor replacement, although this process is time-consuming and expensive" (page 22).
Introduction	"...altered to make it less susceptible to degradation..." I wonder if this is correct. I thought that the modifications to recombinant factor VII were made such that it was spontaneously activated during the manufacturing process. What is the source for this statement?	This statement has been removed from the Report given that its veracity is uncertain.
Introduction	Key Question 2: is it intracranial hemorrhage (taking in intracerebral hemorrhage and other bleeding inside the cranium, like subarachnoid hemorrhage, epidural hemorrhage, etc), or intracerebral hemorrhage? Most (but not all of the ICH literature is in the setting of intracerebral hemorrhage (bleeding into the brain tissue).	Although most studies focus on intracerebral hemorrhage, the analysis was designed to be as inclusive as possible in how it framed this issue, particularly given the limited number of observational studies and clinical trials available. The Report clarifies this further in the background section on intracranial hemorrhage (page 71).
Introduction	The introduction and background makes little reference to the findings from other systematic reviews, and it is unclear to what extent this review has added new or different information in the main conclusions when compared to other reviews. E.g. what lessons can be learned from the analysis of selected randomised control trials as in the AHRQ review, and reviews which evaluate all randomised controlled trials, irrespective of clinical setting, and possibly justified on the basis that the drug is working by a common means of action (see below). Alternative approaches have also included an analysis by prophylactic or therapeutic use, but there is little discussion about this approach in the AHRQ report.	We have included information on past systematic reviews as a context for the report (pages 25-26). We have also noted in the Introduction (pages 25-26) that a description and evaluation of prior systematic reviews is contained in the Discussion section in the section on “Context” (page 184). We have also included an analytic framework in the Executive Summary (page ES-3) and the main report (page 32) that notes the distinction between prophylactic and treatment use. In addition, we also discuss the types of use (prophylactic, treatment, and end-stage) that are pertinent to each indication in respective sections entitled “Place of studies within analytic framework”. The following discussion of prior systematic reviews has been added to the introduction of the Report:
Introduction	Trumpeting the 97% off-label number is completely erroneous, since	In the abstract, executive summary, and main report, the report

	most on-label usage is not in the hospital.	notes that the majority of use is outpatient. The report (including the abstract and executive summary) also clarifies that our focus is largely confined to evaluating patterns of in-hospital rFVIIa use. We also explicitly state that "a majority of rFVIIa use occurs in the outpatient setting and that of the majority of this use in for on-label indications related to hemophilia." In addition, we have edited the title of the report to include the word "in-hospital use" of rFVIIa.
Introduction	The severity of illness of many of these target populations should be emphasized, because this strongly affects clinical decision making.	We have included an analytic framework (in the Executive Summary and in the methods section) within each key question to emphasize the stages during which rFVIIa can be and is used. The available data is not detailed enough to provide information on the decision-making that occurs around the end-stage use of rFVIIa. It is limited to the studies performed. However, we more clearly identify where on the continuum of prophylaxis-treatment-end-stage these studies lie.
Introduction	On pages 2 and 3, the reference to drug companies is somewhat harsh. It is doubtful that manufacturers are reluctant to have additional indications for their drugs studied for fear "that additional studies might reveal unfavorable information. (page 2, line 55. Similarly, the statement that "the pharmaceutical industry seeks enlarged markets to ensure profits and sustain development" should be softened. Page 3, line 76). It is unfair to label all companies as profit-driven over safety-driven.	We have edited our comments to include the following comments: "While supplemental NDAs are an available mechanism for adding indications to an existing approval, manufacturers may not always seek them, particularly if a drug is already being used off-label" (page 20) and "There is a range of conflicting perspectives on off-label use. Payers question the need to pay for unproven products, physicians want autonomy to meet individual patient needs, and the pharmaceutical industry seeks continued return from existing products" (page 21).
Introduction	Page 4, line 24: the "of" should be changed to "or."	We thank the reviewer for catching this error. We have modified the report accordingly.
Introduction	Page 7: I wonder if the first 3 off-label indications could simply be dropped from this report, since the indications are so close to the original intent of the drug and including these adds little to this report.	The report is focused on off-label use and, therefore, provides a thorough listing of off-label uses, even if some are more similar clinically to approved uses. The report describes off-label uses in a list format with the first non-hemophilia indications being relatively clinically similar to on-label uses. We use this format to emphasize that the indications noted further down the list are more distinct clinically.
Introduction	Page 7, line 44: "lack of approval outside the United States" would imply that rFVIIa has been approved for trauma, intracranial hemorrhage, cardiac surgery etc. in the United States. Since this is not the case, this sentence should be restructured.	The report has been modified to clarify that these indications lack approval in the U.S. and elsewhere.

Introduction	Page 8, line 22; "prio" should be "prior"? Same page, line 56: Patient should be plural. Page 14, line 38: a hematologist or hematologists?	We have corrected these errors.
Introduction	I learned a lot about off-label use :).	We thank the reviewer for this comment.
Introduction	• Inadequate contextual representation of patterns of rFVIIa use − The Draft Report fails to meaningfully represent the market trends of other products in related use over the same period of time. We cite the example of antifibrinolytic agents use in cardiac surgery as an illustration: The marketing withdrawal of a potent antifibrinolytic (aprotinin) widely used in cardiac surgery was contemporaneous with significant increases in the use of other antifibrinolytic agents in CABG/valve procedures. While the use of rFVIIa might have increased over the same period, it accounted for only a very small proportion of these procedures in 2008.	The report mentions the withdrawal of aprotinin and the shift towards the use of tranexemic acid in CABG procedures. (page 23)
Introduction	Inherent properties of at-risk population being analyzed • A lack of consideration of the unmet medical needs driving the off-label use of rFVIIa − The areas where rFVIIa is being used off-label raise the possibility that this use is being driven by unmet medical needs. The common element in trauma, ICH and cardiac surgery that drives rFVIIa use is the desire to treat life-threatening hemorrhage in patients unresponsive to standard modes of treatment.	The report assumes the frequent and legitimate occurrence of clinical situations where rFVIIa is being used in an attempt to fill an unmet medical need (indeed, this is encapsulated in our inclusion in the analytic framework the “end-stage” category of use). The rationale for the report is that there is a need to evaluate whether and where this need is successfully filled by rFVIIa. While recognizing the inherent difficulties involved in rigorously evaluating these clinical situation, the report concludes that current evidence is not adequate to determine the answer to this question.
Introduction	Possible impact of concomitant therapy on the occurrence of serious adverse events − While serious adverse events, especially thrombotic events, may be attributable to the pro-thrombotic effect of hemostatic agents such as rFVIIa, they may also be attributable to concomitant therapies.	The report acknowledges that the presence of other elements of care may have a profound effect on the favorable and unfavorable outcomes associated with rFVIIa. For example, discussions of the evolution of “usual care” are included at the beginning of each Key Question by indication in sub-sections entitled, “Usual care during the time frame of included studies”. The evolution of usual care includes many examples of modified approaches that might alter these outcomes. This evolution of usual care makes interpretation of studies with different schemes of usual care more difficult.
Introduction	Indication/trial specific issues in analysis methodology • Trial designs, endpoints and regulatory constraints − Despite exhaustive discussions with regulatory authorities worldwide, it has not been possible to obtain endorsement for a trial that examined the primary endpoint: “Does rFVIIa stop or significantly slow life-threatening hemorrhage?” The primary reasons are that it is impossible to develop an acceptable and broadly reproducible method	The report acknowledges that studies assessing late use of rFVIIa are very difficult to design and implement. This creates an unfortunate mismatch between use of the product in hospitals and the available evidence that fails to capture this particular mode of use. The report continues to emphasize this mismatch and caution against generalizing from studies involving earlier use of rFVIIa to situation where rFVIIa is used

	of assessing whether operative bleeding has slowed or stopped, and that, until the recent appreciation of the dangers of blood or blood component transfusion (particularly in the setting of cardiac surgery), hemorrhage has been widely regarded as a manageable medical problem.	as an end-stage measure.
Introduction	Patients with hemophilia with long-term inhibitors constitute a small but significant portion of the estimated 18,000 patients with hemophilia A or B in the United States. However, between 15% and 30% of patients with hemophilia A develop inhibitors to Factor VIII, and between 2% and 5% of patients with hemophilia B develop inhibitors to Factor IX at some time in their clinical course. 5 Thus, the statement that "the majority of hemophilia patients never require rFVIIa for bleeding" is misleading. While some of these patients and particularly those with lower inhibitor titers can be eventually "tolerized", there remains a group of between 800 and 1200 patients with high titer inhibitors who rely on bypassing agents, such as rFVIIa, to treat frequent bleeding episodes and to allow for surgical and dental procedures. The majority of patients with hemophilia or other bleeding disorders typically receive their coagulation factors directly through specialty pharmacies, home healthcare companies, or 3408 programs run by hemophilia treatment centers. The Premier database does not take into account any of these distribution channels, as it only considers the number of hospital discharges. While there are no data from sources such as IMS Health Inc. to monitor rFVIIa use on a per-patient basis, these direct-to patient distribution channels are only used for patients with hemophilia or other bleeding disorders. Based on the 2008 sales data for Novo Nordisk, approximately 50% could be attributed to specialty pharmacies, home care and 3408 programs, while approximately 20 % could not be assigned to a specific identifiable channel.	The Report's current statement that "most hemophilia patients never require rFVIIa for bleeding episodes" (page ES-1) is consistent with the manufacturer's data that 1,200-1,800 of 18,000 U.S. hemophilia patients (7-10%) require rFVIIa. The report focuses on in-hospital use of rFVIIa. The report notes that a majority of rFVIIa use occurs in the outpatient setting and that a majority of outpatient use in for on-label indications related to hemophilia.
Introduction	1.1.2 Inadequate contextual representation of patterns of rFVIIa use. While the Draft Report presents information on the trends in rFVIIa use over the past decade, it fails to meaningfully represent the market trends of other products in related use over the same interval. We use here the example of cardiac surgery, which is cited as having the highest area of off-label use, to illustrate the profound practice changes that may have influenced the use of rFVIIa over the past few years. Aprotinin (Trasylol, Bayer AG) was approved for the reduction of bleeding in surgical procedures, including cardiac surgery, based upon initial studies correlating reduction in bleeding with improved mortality. The possibility that aprotinin use might also be associated with end organ damage and increased mortality was first convincingly raised in two seminal papers in 2006 and 2007.8, Subsequently, the FDA issued	While it is beyond the report's scope to present trends in other hemostatic products, the report notes the possible role that discontinuation of aprotinin use may have had on trends in use of hemostatic agents (page 22) and notes that all included studies were completed by November 2007 (i.e., prior to removal of aproprotinin from the U.S, market) (page 133).

	multiple advisories, and in November 2007, Bayer suspended marketing of aprotinin, resulting in a significant drop in use and ultimately in its removal from the market. 1° There was a subsequent increase in the use of other antifibrinolytics (mainly epsilon aminocaproic acid [Amicar, EAA], and to a lesser extent tranexamic acid [TAI), as well as rFVIIa (see Figure 1, based on data drawn from the Thompson Reuter Market Scan Hospital Discharge database). Tranexamic acid is not marketed in the United States. Neither of the substituted lysine analogs (TA or EAA) is as effective as aprotinin in reducing pen-operative heart surgery bleeding. However, even though the use of rFVIIa might have increased over this period, it still accounted for a very small proportion the coronary artery bypass graft (CABG)/valve procedure discharges in 2008 (see Figure 2).	
Introduction	1.3 Indication/trial specific issues in analysis methodology 1.3J Trial designs, endpoints and regulatory constraints. The published data have reported that in situations of hemorrhage judged by clinicians to be desperate or life threatening, the acute administration of rFVIIa in these circumstances has stopped or significantly slowed the bleeding with sufficient predictability that physicians have continued to use the drug. The first illustration of this use was in an Israeli soldier with multiple penetrating injuries, who was exsanguinating from refractory bleeding before rFVIIa was administered, which allowed for stabilization and subsequent surgical treatment.25 Since physicians have reported on and demonstrated the potential use of rFVIIa for treating bleeding episodes in life-threatening situations outside the approved clinical indications, Novo Nordisk has undertaken several randomized clinical trials of rFVIIa as part of a development program directed for regulatory submission. However, despite exhaustive discussions with regulatory authorities worldwide, it has never been possible to obtain endorsement for a trial that examined as a primary endpoint the question: “Does rFVIIa stop or significantly slow life-threatening hemorrhage?” There are many reasons for this impasse, but two are most prominent. The first is that it has been impossible to develop an acceptable and broadly reproducible method of assessing whether operative bleeding has slowed or stopped. The second is that until the recent enhanced appreciation of the dangers of even modest amounts of blood or blood component transfusion (particularly in the setting of cardiac surgery), hemorrhage has been broadly regarded as a manageable medical problem, provided that an adequate supply of replacement products could be secured. The relative safety of the act of transfusion itself has only relatively recently been called into question2629, but concerns continue to mount and it is against this background of concern that we	The report’s goal is to inform physicians so that their practice choices may reflect the state of evidence around rFVIIa. In particular, it is critical for physicians to recognize that the ability of rFVIIa to produce cessation of bleeding does not necessarily equate with improved patient outcomes. The report distinguishes outcomes that are direct and indirect based on whether the outcome relates to the vital or functional status of patients. The endpoint of “Does rFVIIa stop or significantly slow life-threatening hemorrhage?” is categorized as an indirect or surrogate outcome because it relates to the process of care and the pathophysiology of injury, but not to what ultimately happens to the patient. While the assumption that cessation of bleeding should lead to better direct patient outcomes has a common sense appeal, current evidence does not consistently demonstrate improvement in patient outcomes, as noted in the report (page 181).

	believe the evaluation of a therapy that can stop or slow hemorrhage should be conducted. Indeed, the ongoing use of rFVIIa by physicians faced with life-threatening hemorrhage despite the risks and the acquisition cost testifies to the extent of this unmet medical need. In the trials that have been designed, not only has it been necessary to work with a broad variety of surrogate endpoints to assess the ability of rFVIIa to stop bleeding, there are grounds for believing that the patients actually studied in comparative trials are not properly representative of the real-world situations in which rFVIIa has been used. A case in point is the recently published Novo Nordisk sponsored Phase 2 cardiac trial (F7CARD-1610)12, in which 172 patients were studied. This was a vii cardiac surgery study done in the post-operative ICU setting. The qualifying bleeding rate was an hourly loss of 200 ml/hr for at least 30 minutes. From the outset of the trial, it was recognized that this was not a rate of blood loss that would necessarily prompt a majority of clinicians to prescribe off-label rFVIIa. Further, this trial was designed primarily as a safety and proof-of-concept trial. Despite a relatively low bleeding-rate threshold, and the involvement of over 50 centers worldwide, it took almost three years to enroll these 172 patients. During this time, over 2,500 patients pre-operatively identified as being at high risk for postoperative hemorrhage were screened and consented, but never reached the bleeding threshold. Thus, approximately S% of screened patients were actually dosed in the trial. This is still a much higher usage rate than the estimate of 1.5% of rescue therapy in the “real world” and the differences in outcome underline this. The mortality for off-label use observed in the AHRQ Draft Report is 27%; in the F7CARD-1610 trial the mortality was <11°h. Remarkably, although this trial was not powered for efficacy, 25% of placebo patients required re-exploration for bleeding within the first 24 hours, which was double the rate for the rFVIIa-treated group. This pre-defined endpoint was statistically significant at p=0.03. The higher rate of re-exploration in the placebo group, compared with more commonly reported re-exploration rates of 3-8%, underlines the fact that this was a population of significantly bleeding patients, even though they were not in the extreme state more typical of cardiac rFVIIa usage outside of clinical trials. Notably, no deaths occurred among the rFVIIa-treated patients who underwent re-exploration for bleeding. This was not true of the placebo-treated patients.	
	Methods	
Methods	Given Danish manufacturing company, limiting search to English language is debatable.	The Report clarifies that the search strategy was not limited to English language, so our search did find non-English language

		articles on the key questions 2 to 4, including one RCT, comparative observational studies and six case reports. We have included a brief description of these non-English language studies in the Report (page 48), along with a full table in the Appendix (Appendix Table 5, page A-78).
Methods	Decision to rely on risk difference as main metric for analysis in systematic review unusual and not explained	We describe the considerations surrounding our decision to use risk difference in the methods as follows: “The risk difference was chosen as a measure of effect size for the report because it is easy to interpret and the risks for different outcomes were similar across studies, such that the disadvantages of using the risk difference approach to estimate effect size (e.g., as compared to other common metrics such as the odds ratio) were minimized.” (page 45)
Methods	The patterns of use are derived from the Premier Database, but it could be described in more detail in the beginning, including acknowledgment of strengths and limitations (e.g. the data is clearly skewed to a small number of high usage hospitals), and whether this information differs from the findings reported in other international databases of patterns of use.	The Premier database is nationally representative in terms of hospital characteristics. There is no indication that the sample of hospital oversamples hospitals that are high-end users of rFVIIa. The report acknowledges specific limitations of the Premier database within the “Limitations of the Premier Database Analysis” section of the Discussion (page 187).
Methods	Data sources for this review draw on registries, cohorts, randomised control trials and comparative and non-comparative studies. More justification is required for the cut off of 15 or more patients for these later studies, and for the approach of the quality of assessment for comparative observational studies which was "based primarily on expert consensus amongst the team members."	We have added information within the methods sections of both Executive Summary (page ES-5) and main report (page 37) about the sources used to derive our criteria for assessing RCT quality and comparative observational study quality. We have also provided information on our rationale for limiting the comparative observational studies to studies with 15 or more patients, namely that the likelihood of biased reporting is likely to increase in smaller reports (page 35).
Methods	Data extraction/quality assessment p44. Either here or in the results some indication of the level of disagreement in decisions would be helpful. Ideally inter-rater reliability assessments could be presented. However accepting that there are only rarely time and resources to do this, a general comment may be all that can reasonably be expected.	We have included a narrative description of the criteria that were used and also summarized the number of disagreements and how “far apart” they were on the categorical scale (good, fair, poor) (page 48)
Methods	Analysis of comparative studies p50. The decision to focus on just risk difference in dichotomous outcomes is unusual and requires justification. Odds ratios would probably be most analysts first choice and most likely to yield consistent patterns across studies if they exist (accepting that all metrics should be considered). The decision to focus on risk difference led in turn to a very unusual way of presenting risk difference - arcsin difference. Even if the reason for this choice is correct, most readers will not be familiar with its interpretation, and	As explained above, we have provided a full explanation for using risk difference and also report this summary statistic for all meta-analyses, along with the arc sine summary statistic in the appendix. “The risk difference was chosen as a measure of effect size for the report because it is easy to interpret and the risks for different outcomes were similar across studies, such that the disadvantages of using the risk difference approach to estimate effect size (e.g., as compared to other common

	some efforts to back transform to a more commonly used metric (simple risk difference or even NNT/NNH) would be demanded.	metrics such as the odds ratio) were minimized." (page 45)
Methods	Setting out a strategy for investigating heterogeneity should have been considered at the outset. Investigations of heterogeneity may have been overlooked. However the reporting of heterogeneity makes it difficult to assess whether such analysis was appropriate.	We have described our assessment of heterogeneity in the section titled "Clinical considerations of Heterogeneity" (page 26). The Report's Introduction section continues to have a sub-section on "Special subgroups within trauma and cardiac surgery" that explains why we separated out body from brain trauma and adult from pediatric cardiac surgery in our analyses (page 27). We have also included in the Methods section a description of the heterogeneity statistic used and our approach to heterogeneity (page 44). We have also addressed issues of heterogeneity by including sub-sections discussing heterogeneity as part of the background for each respective indication (see sections titled "Issues of Heterogeneity" in each key question). In addition, we describe the criteria for combining certain studies on a given indication when the patient population or aspects of treatment differed. We also describe these heterogeneity results, in addition to presenting these statistics in the figures, within the results sections for each key question, as appropriate.
Methods	Re: scoring of affiliation with the company. While noting that Novo Nordisk funded most of the trials and may therefore have biased the results is appropriate, it is also worth noting that Novo Nordisk was generous and scientifically appropriate in funding many trials AFTER off-label use in those areas was already underway. Trial funding can be looked at as a marketing tool (it certainly started that way in trauma) but is also part of due diligence on the company's part to learn as much as they can about the drug.	We recognize the possibility of overemphasizing financial support of clinical research, particularly when no other prominent sponsors have a committed interest in pursuing such studies. Nonetheless, the report mentions the degree of financial support provided by the manufacturer for the various studies (as applicable). In the Introduction, we have included a brief description of the advantages and disadvantages of corporate involvement in clinical trials (page 26).
Methods	Types of Evidence, Overview of comparative off-label studies, second paragraph, page 15: Why did the reviewers use studies on use of off-label rFVIIa separate from the five indications of interest for comparative effectiveness? Could this paragraph explain this a little better?	We have explained more fully that Key Question 1 provides an overview of off-label use of rFVIIa and that Key Questions 2 through 4 focus on selected clinical indications of off-label uses in greater detail. We have explained this earlier in the Introduction (page 19), as well as where the scope and purpose of each Key Question are also described (page 27).
Methods	Quality rating for observational studies: could the authors use more established rating tools, or the current EPC methods, instead of basing on expert consensus?	We have provided additional information in the Methods section about the sources used to derive our criteria for assessing the quality of comparative observational studies, as well as RCTs. (page 37)
Methods	Page 18, line 14-18, different criteria were used by different designs -- state the rational of doing this?	We have provided additional details regarding the rationale for selecting particular criteria for different research designs. (page

		37)
Methods	Table 5, strength of evidence: That risk difference crosses zero does not necessarily mean that an estimate to be imprecise, since when an intervention has no effect on an outcome, the effect measure would likely to have a 95% CI crossing zero in the reasonable range of sample size.	The report follows the logic suggested by the reviewer. Estimates that cross the null may be relatively precise or relatively imprecise. Null assessments that are relatively precise are those where the statistical estimate has small confidence intervals and where strength of evidence is strong (meaning that design weaknesses are limited). Null assessments are relatively imprecise, either due to substantial statistical uncertainty or poor study quality and strength of evidence. The report follows the strength of evidence guidelines provided to the Evidence-based Practice Centers for this type of table. (Owens DK, Lohr KN, Atkins D, et al. Grading the strength of a body of evidence when comparing medical interventions-Agency for Healthcare Research and Quality and the Effective Health Care Program. Journal of Clinical Epidemiology. e-pub ahead of print July 2009)
Methods	Page 22, line 31-34, no formal statistical comparison was conducted to detect the magnitude of differences.	The report did not intend to compare directly the patients included in the Premier database with those presented in published studies. We have modified our language to reflect that a formal statistical comparison between Premier and study patients was not intended (page 45). Characteristics of the Premier population are reported to allow for qualitative comparisons with the populations in the included studies.
Methods	Line 36: In addition to weight, are there any other variable, such as strata, that needs to be used to have a national representative estimates? For example, the use of rFVIIa may be different across regions? Does the hospitalization weights apply to non-hospitalized encounters? Would it be possible not to consider non-hospital encounters instead of using a possible inappropriate weight?	The sample provided by Premier is designed to be nationally representative by bed size, geographic location (i.e., region), designation as urban versus rural, and teaching status (academic versus non-academic). The weights were used to adjust for the increasing number of hospitals included in the Premier sample over time. In the Results section, variation in rFVIIa use across regions of the country is presented. The data are representative without statistical manipulation beyond use of the statistical weights provided by Premier. We do not have data on non-hospital encounters.
Methods	Analysis of comparative studies: 1) Define what were “sufficient studies.”	We have clarified the definition of “sufficient” by adding this statement: “We defined sufficient studies (for a given indication) as a total of at least two studies of fair or better quality, including at least one study of good quality.” (page 44)
Methods	2) How does clinical and methodological diversity influence the decision of combining studies? Need to state this in this section.	Regarding methodological diversity, the report combined studies regardless of study type (RCT versus comparative

		observational) as long as they met the quality criteria of being good or fair. Regarding clinical heterogeneity, the report combines only those studies that had similar patient populations in terms of baseline clinical characteristics. These issues are now clarified in the Methods sections "Analysis of comparative studies: Statistical analyses" (pages 44-45)
Methods	3) Arcsine method may have its technical advantage to combine studies. However, the resulting summary measure lacks easy and clear clinical interpretation and is not helpful for the consumers of CERs to understand the results on benefits and harms, and to aid decision making. For conducting CERs, we don't recommend the use of this measure. Since there are not many MAs performed in this CER, it would be better to change the measure to risk difference or relative risk for MAs.	As noted above (in response to comments by other reviewers), the advantages and disadvantages of different metrics are discussed in greater detail within the report. We present both risk difference analyses (main body of report) and analyses using the arc sine method (Appendix) to allow for easier interpretation of results by readers.
Methods	4) It would be helpful to present an I2 for the magnitude of heterogeneity, too	We have presented both the Q-statistic and the I2 for each of the summary figures that are presented.
Methods	5) The authors should explore heterogeneity when present.	As noted above, we have included a qualitative discussion of heterogeneity for each indication, where appropriate.
Methods	Analysis of non-comparative studies Specify the methods used to compare the differences, whether qualitatively or quantitatively.	We have modified our language to state that differences are "reported," rather than "compared."
Methods	Omission of outpatient or home use of rFVIIa in hemophilia patients from analysis − Although the AHRQ Draft Report acknowledges the exclusion of outpatient on- label use, it is not until page 146 that this appears. We believe that this acknowledgment also belongs in the Abstract and Executive Summary of the Draft Report.	We have clarified early on in multiple places in the abstract (page vi), executive summary (page ES-3) and main text (page 42) that its assessment of off-label use is limited to inpatients. We have also acknowledged that a majority of rFVIIa use occurs in the outpatient setting and that of the majority of this use in for on-label indications related to hemophilia (see immediately below). Furthermore, we have edited the title of the report to read as: Comparative Effectiveness of Recombinant Factor VIIa for In-Hospital Off-Label Indications versus Usual Care.
Methods	−The on-label administration of rFVIIa for bleeding in patients with hemophilia A or B with inhibitors occurs primarily in the outpatient setting in clinics or at home, whereas patients with acquired hemophilia or FVII deficiency may be treated in both the in-hospital setting and non-hospital setting. Any analysis seeking to determine the patterns of rFVIIa use must consider both the in-hospital setting, as well as the outpatient and home settings. Most patients with hemophilia receive rFVIIa from specialty pharmacies, home healthcare companies, or 340B programs run by hemophilia treatment centers.	The abstract (page vi), executive summary (page ES-7) and main text of the report (page 58) note the context of rFVIIa use, including that the majority of use is outpatient and that a majority of outpatient use is related to hemophilia. As described above, the report also emphasizes that it focuses only on in-hospital applications of rFVIIa. The report also notes within the methods and results sections that the unit of for the Premier database is that of hospital cases—that is, any use of rFVIIa during a given hospitalization. We favored the use of this

	− Further, the Draft Report uses the number of discharges as a surrogate measure of rFVIIa use, and by doing so ignores the large volume of on-label inpatient rFVIIa use in a small number of patients with hemophilia with inhibitors or FVII deficiency.	case-based unit of analysis because of its advantages, particularly because it captures the medical decision-making component of care about whether to use or not use rFVIIa for a given patient. Alternative methods of analyzing rFVIIa use by dosing also were examined, including the number of times rFVIIa was dispensed by the inpatient pharmacy and the total dose of rFVIIa dispensed. We determined that these strategies of examining dosing had significant drawbacks, including: 1) possible discrepancies between dispensed rFVIIa and the amount actually administered to the patient, 2) lack of consistent hospital coding of rFVIIa dispensing (e.g., missing or variable reporting of units (such as milligrams dispensed versus vials dispensed)), and 3) statistical problems associated with the presence of outlier cases with numerous doses and large aggregate dosage. Examination of the dosing information also indicates substantial variation in the dose of rFVIIa dispensed during individual hospitalizations with some cases being dispensed a fraction of a 1.2 mg vial while others received more than a hundred vials. Individual cases with large aggregate dosages included both hemophilia and non-hemophilia cases. This rationale for our approach is described in a new methods sub-section on the Premier database analyses entitled “Unit of Analysis” (page 43)) The report also specifies the unit of analysis in the results. (page 58).
Methods	Systematic Review __• Inappropriate pooling of results from studies with disparity in trial design, endpoint and sample size − Hemorrhages occurring in different clinical settings are not comparable. The pooling of dose-escalation studies with Phase 2 or Phase 3 studies in the efficacy analyses is a systematic error made in numerous locations within the document.	The report acknowledges in multiple places that the issue of clinical homogeneity of pooled studies requires care and consideration (see, for example, the introduction (page 26) and methods section “Issues of Heterogeneity” (page 44)). As noted above, defining any particular level of clinical specificity will involve advantages and disadvantages. The report disagrees with the concept that Phase 2 and 3 studies should necessarily be analyzed separately. When sufficient data of suitable quality is available to allow pooling, a summary effect of rFVIIa on the outcomes of interest has been estimated. For each indication, the Report includes a section discussing heterogeneity and specifying the reasoning behind decisions to pool, or not pool, studies (see specific sections for each indication entitled “Qualitative Considerations of Heterogeneity”, for example, page 72).
Methods	L1.1 Omission of outpatient or home use of rFVIIa in on-label use from analysis	As noted above, the report clearly states our focus as being solely on in-hospital use, and also notes the context of rFVIIa

	The Draft Report states that the rate of approved use is limited to 2.7%. This figure is incorrect and misleading. Although it is not possible from current data to clearly distinguish between on-label and off-label use (although on-label use is much better known), the best estimates based on available data and patient models suggest that off-label use represents approximately l52O% of drug volume. The highest estimate of off-label use that is consistent with any current data (including the Premier database) is certainly less than 25%. This high estimate would assume that all patients receive an average dose of 90 mcg/kg body weight. This is a very liberal assumption, given that for cardiac surgery, case reports typically indicate usage of 2040 mcg/kg. Even usigthe higher percentage, it is clear that the increased use of rFVIIa is not "solely due to rising off-label use". This is not possible, with more than 75% of current use being on-label. We present our rationale here for this argument. The Draft Report is based solely on data from the inpatient administration of rFVIIa. It omits any consideration that on-label administration of rFVIIa for bleeding in patients with hemophilia A or B with inhibitors occurs primarily in the outpatient setting in clinics or at home. Patients with acquired hemophilia or FVII deficiency may be treated both in the in-hospital setting and in the non-hospital setting. Any analysis seeking to determine the patterns of rFVIIa use must consider both the inhospital setting as well as the outpatient and home settings. Over the past decade, treatment of hemophilia has evolved from a hospital or hemophilia treatment center (HTC) focused approach to one in which the majority of patients and bleeding episodes are now treated in the home setting.	use. The report notes that the majority of total use occurs in outpatients and that a majority of outpatient use is related to the FDA approved indication of hemophilia. Nonetheless, in-hospital U.S. sales of rFVIIa are estimated to be $138.5 million in 2007 (http://drugtopics.modernmedicine.com/drugtopics/data/articlestandard//drugtopics/262008/526563/article.pdf). This is a significant amount of in-hospital use, particularly considering the enormous variation in rFVIIa use between hospitals.
Methods	The Draft Report incorrectly uses the number of discharges as a surrogate measure of rFVIIa use. The vast majority of off-label use involves a one-time effort to stop or decrease bleeding (e.g., in ICH, trauma or cardiac surgery). As the Draft Report points out, this one-time dose may be as low as 5 mcg/kg. Despite their relatively small populations, rFVIIa use by patients with hemophilia with inhibitors or FVII deficiency typically involves high doses, as well as multiple doses of rFVIIa, at an average dose of 90 mcg/kg every 2 hours (hemophilia with inhibitor patients) or 15-30 mcg/kg every 4 to 6 hours (EVII deficiency patients). In some cases, such as in pen-operative use, treatment may be required for several days. For example, treatment of bleeding in orthopedic surgery patients with hemophilia with inhibitors has been reported to last as long as 17 days and to require as many as 128 doses of 90 mcg/kg over that time period.6' 7 Central nervous system bleeds in patients with hemophilia with inhibitors are treated most often for 14-21 days with routine dosing. Thus, even in the	The report analyzes patterns of in-hospital rFVIIa use. The report focuses its analysis on the hospital cases as the unit of analysis. As described above, we favored the use of this case-based unit of analysis because of its advantages, particularly because it captures the medical decision-making component of care about whether to use or not use rFVIIa for a given patient. Alternative methods of analyzing rFVIIa use by dosing were also examined, including the number of times rFVIIa was dispensed by the inpatient pharmacy and the total dose of rFVIIa dispensed. But we determined that these strategies of examining dosing had significant drawbacks, including: 1) possible discrepancies between dispensed rFVII and the amount actually administered to the patient, and 2) lack of consistent hospital coding of rFVIIa dispensing (e.g., missing or variable reporting of units (such as milligrams dispensed versus vials dispensed)), and 3) undue influence of outlier

	hospital setting, the number of patients discharged does not reflect the volume of product used and its share of total rEVila use.	cases who were dispensed very large doses. Examination of the dosing information also indicates substantial variation in the dose of rFVIIa dispensed during individual hospitalizations, with some cases being dispensed a fraction of a 1.2 mg vial while others received more than a hundred vials. Individual cases with large aggregate dosages included both hemophilia and non-hemophilia cases. This rationale and decision-making is now described in a new methods sub-section on the Premier database analyses entitled “Unit of Analysis” (page 43).
Methods	L1.4 Inappropriate pooling of data from trauma and non-trauma centers. The data on the trauma indication presented in the Draft Report are misleading with respect to the usage of and mortality patterns with rFVIIa use. The Premier database does not discriminate between designated trauma centers and non-trauma centers. The mortality and case-mix of patients in these two types of treatment centers are markedly different. As an illustration, the mortality rate described in the Premier database (36% mortality in 3639 bodily trauma uses in 2008), is higher than those reported in many current trauma series. One possible reason for this discrepancy is the inclusion of data from both trauma centers (which have lower mortality rates) and non-trauma centers (which have higher rates of mortality).’4 Therefore, the Premier database is neither a useful nor informative source of data on trauma.	The report discusses issues related to heterogeneity of patient populations in the studies within a new section for each indication entitled, “Qualitative considerations of heterogeneity,” and the body trauma section specifically discusses this concern (page 97). In multiple locations, the report notes that Premier patients may differ in important ways from study patients, and data from the Premier patients is not pooled with data from published studies. The body trauma studies all evaluate data from either level 1 trauma centers or military trauma registries, with the possible exception of the Boffard RCT, which was conducted in 32 hospitals in multiple countries and which does not report in the associated publication whether these were all the equivalent of major trauma centers.
Methods	Systematic Review Overview The systematic review of the off-label studies of rFVIIa is flawed for several reasons. Erroneous assumptions are made that hemorrhage occurring in different clinical settings is comparable. The results from studies with disparity in sample size, heterogeneity in trial design and endpoint are pooled. There is a systematic error made in numerous locations within the document where dose-escalation safety studies are used in efficacy analyses. Further, conclusions regarding the benefit or lack thereof from the use of rFVIIa are drawn in situations that had potential confounding factors. Unfortunately, the two large, randomized controlled trials on the efficacy and safety of rFVIIa in cardiac surgery1 and trauma3° were not published at the time of this review. In light of these factors, the validity of the evaluations from this review is questioned.	The report notes that the issue of clinical homogeneity of pooled studies requires care (page 26). As noted above, defining any particular level of clinical specificity will involve advantages and disadvantages. Care is needed in the use of information derived from dose-escalating studies because very low doses of any drug may be functionally equivalent to placebo. The report includes all studies making use of rFVIIa for two reasons: 1) no dose-response relationship is demonstrable in our analysis, and 2) this provides the greatest statistical power to detect a positive or negative effect of rFVIIa. When data are available to allow pooling, the effect of rFVIIa on the outcomes of interest has been estimated. As described above, for each indication, the report includes a section discussing heterogeneity and specifying the reasoning behind decisions to pool, or not pool, studies.
Results	"Study patients were younger and had lower clinical acuity in comparison to patients receiving rFVIIa in US hospitals." I don't understand the comparator. Where were the study patients studied? Outside the US? Or does this mean the patients who were on the	The comparison is between the patients represented in published studies (RCTs and comparative observational studies) and the patients represented in the Premier data. This section of the report has been re-written to make this

	studies were younger/less sick than the patients getting rFVIIa in off-label settings?	comparison more clear (page 64).
Results	In general, I do not understand the term "arcsine summary effect size" used in nearly all the figures. I asked other statisticians and epidemiologists about this term, and it was something they were not familiar with, either. I thing some explanation of this term is required for a general audience that is the target of this report.	We have included a better explanation of the arc sine statistic (in both the Executive Summary and Report), including its strengths (loses the least amount of statistical information) and weaknesses (it is less well known, see page 45 in the methods section of the main report). There are important technical advantages of this method, particularly where the outcomes of interest are rare and no events are observed in both arms of a trial. The arc sine method includes information from such trials while the risk difference method does not. The report contains both the risk difference (in the main report) and arc sine summary statistic (in the appendix). The results for both metrics show consistent findings.
Results	Presentation of some tables and figures difficult to follow. Poor linkage between data as reported in original studies and the results reported in the meta-analysis.	The forest plots in the Report have been improved by including additional information on these plots. This provides more of a context for interpreting the information within the plots themselves.
Results	The reporting of the results of the included studies is not as accomplished as other aspects of the report. An obvious issue is the need to continually refer back to Fig 5 & 6 p 90 when considering the results for key questions 3-4 pp 96-153. It would be useful to have a graphical summary of the results of all outcomes for each question, even at the expense of repetition which I think is justifiable in a report of this length.	We have addressed this comment by simplifying the process of locating key information between tables and by including an overall tabular summary of the studies considered in the report (Table A in Executive Summary, page ES-14). The report focuses on highlighting the most relevant information. Graphical representation of the direct patient outcomes has been prioritized over graphing outcomes that are indirect and subject to multiple problems of interpretation.
Results	It is also extremely difficult to relate the results of the included studies as summarised in the report back to the raw data in the included studies. Try to work backwards from the data in Figure 5 to the actual numbers of deaths recorded in the treatment and control arms of each of the four included studies for ICH. It's difficult. Most forest plots allow this to be reasonably easily achieved.	As we note above (in our response to a prior comment by this same reviewer), we have included additional information within the forest plots, so that key information is presented along with the study-specific effects.
Results	A further limitation of Fig 5 is that the summary measure is not presented on the graph so it is difficult to see how this relates to the results of the included studies. This is important in an initial consideration of whether there is heterogeneity.	In the figure referred to by the author (Figures 7 to 18 in the report), we have presented the summary point estimate for those indications with sufficient evidence of suitable quality to warrant the calculation of a summary effect (body trauma and adult cardiovascular surgery).
Results	Very nice commentary on the plateau in usage in trauma. As the longest running off-label users, trauma centers have mostly matured in their use of FVIIa. It is included in massive transfusion protocols, but	In the body trauma section, the report reflects the concept that users of rFVIIa may have evolved in their use of rFVIIa and other products as they have gained experience with the use of

	not given indiscriminately. It was also good to note that 1:1:1 resuscitation has decreased the need for FVIIa. This is certainly the case in our practice.	the drug, as well as the treatment of patients with the acute coagulopathy of trauma (page 96).
Results	On page 39, the authors refer to the "Top 10" hospitals. This could be interpreted in a number of ways: best hospitals, largest hospitals etc. Please define what is meant by "top 10" or use another term.	We have modified our language to clarify that “the ten hospitals with the highest number of uses by discharge accounted for 46 percent of all rFVIIa use.” (page 62) The presentation of information on this subset of hospitals indicates the extreme variation in rFVIIa use.
Results	On page 52, line 40, should there be another word after deemed???	We have corrected this omission and inserted the words “fair quality.”
Results	On page 72, I think that the censorship of early deaths by both the Boffard study and the Spinella study in trauma need to be emphasized to a greater degree. This fact truly colors the results.	We have emphasized this design feature to a greater extent by adding the phrase “which may bias the results” to the conclusions.
Results	On page 82, the potential to inflict harm using rFVIIa in patients with cerebral vascular trauma also needs to be emphasized to a greater degree.	We have addressed this issue in the “Other considerations” section with the following sentence (page 113): “Other authors have raised concerns regarding a subgroup of patients who might have the potential for increased harm with rFVIIa administration. These are patients who have experienced blunt trauma to the cerebral vessels and thus may already be at increased risk for post-traumatic cerebral infarction.”
Results	Figure 3, page 37 is difficult to read. The symbols are too close in size to distinguish between each other.	Given the large number of figures, the report presents several figures in a size that is smaller than optimum. The data contained in Figure 3 are also provided in later figures that display use by individual indications.
Results	Page 35: It would help the readers if the authors state clearly (again) that the numbers are weighted estimates so nationally representative.	As requested, we have included this information.
Results	Page 35, line 19 and 20, provide exact numbers here?	We have provided exact numbers.
Results	Page 38, age and gender distribution: a table or a figure could be a better way to present the results.	We have included information on mean age for each of the indications in Table 16, as this characteristic is most predictive of outcomes, whereas gender is less predictive.
Results	Page 39, when sensitivity analyses were done, mention them in the methods section, too.	We have described in the Methods section that sensitivity analyses were conducted regarding the hierarchy used to define indications within the Premier analyses (page 42).
Results	Page 40, lines 14-20: maybe it is better to refer to the results table to comment on the difference, than looking at two individual studies?	The report text points out a prominent difference between the comparative studies and the Premier data set, and also refers back to the table that also contains information on other studies.

Results	Page 53, so different dosages were combined in the MA? If, state clearly and the rationale.	We have provided clarification in the Methods section regarding different dosages being included in the ICH meta-analyses and the rationale behind the decisions regarding these (page 44-45). We have also provided a reminder regarding these considerations when reporting the outcomes for ICH (page 73).
Results	Page 54, Poor modified ranking score -- Ranking instead of Rankin. -- It helps to state more clearly that it is a binary variable.	The text is correct, as written. “Modified Rankin score” denotes the severity of neurological impairment.
Results	Page 54 Thromboembolic events: A P-value of 0.005 for heterogeneity does not automatically invalidate a combined estimate. On the other hand, if you think the studies are too heterogeneous to be combined, don't do a MA. The validity of a combined estimate should not be judged only based on the p-value of test for heterogeneity.	We have modified the report to reflect this comment. However, the risk difference and arc sine analyses, now done for the specific dose ranges, fail to identify evidence of heterogeneity among studies for any of the measured outcomes.
Results	Page 103: Summary effect size is a very uninformative term due to the use of arcsine measure.	As noted above, the main body of the report presents risk difference analyses, which are easier to interpret, but in all cases also provides the arc sine standardized mean difference in the appendix.
Results	When a MA is conducted, it is also helpful to report the results on test of heterogeneity briefly.	We have provided information on the Q and I^2 statistics where appropriate.
Results	Since the usual care evolves with time and may be very different across study sites, some insights about how this could affect the effect measures would be very helpful.	We have added discussions of the evolution of usual care as it relates to estimating the effect of rFVIIa within the Introduction section “Areas of Anticipated Challenge: Comparisons to Usual Care” (page 26), as well as at the beginning of each Key Question for the selected indications—in sub-sections entitled “Usual Care During the Time Frame of Included Studies.”
Results	Since many observational studies were conducted in US, do any of these studies happen to use the premier database? Any potential influence on the synthesizing results, if so?	The Premier data almost certainly includes cases also included in published studies. The identity of the included hospitals, however, is confidential. Although it might be logistically feasible to identify some Premier hospitals, this was not attempted due to ethical concerns, as well as our contractual obligations with Premier. The report does not synthesize the Premier and comparative study data.
Results	Figure 3 and Figure 4: what is the difference between the two figures -- could not tell based on the captions of the figures.	We have clarified the distinction between these two figures by adding a footnote at the bottom of Figure 4 (page 60).
Results	Figures 10: For SMD, just call it SMD instead of risk difference.	The report has been modified to reflect this suggested change.
Results	Figure 19-20: the marker and the bars for point estimates and 95% CIs are not clear. Also, the styles of the plots are very different.	The figures have been modified to be more consistent and readable (pages 173-179).

Results	Tables 14 and 15: provide 95% CI for the percentages	We have not intended to present the percentages as comparisons, but as a description of the use of rFVIIa.
Results	• Failure to accurately assess denominators pertaining to frequency of rFVIIa use − The Draft Report should not conclude that the off-label use of rFVIIa is "common", as the denominator of total discharges by diagnosis or procedure in the Premier database is unreported and the estimated uses are infrequent when placed in the context of published estimates of the relevant denominator.	The language in the report has been modified and no longer notes these uses as "common." As noted, the report also provides the context of outpatient use of rFVIIa. The report acknowledges the reviewer's comment that the Premier data available did not allow the derivation of denominator data and the calculation of the relative frequency of rFVIIa use among all hospital cases of a specific indication (page 43). Such analysis is beyond the scope of the Report.
Results	• Waiver of consent for clinical investigations in emergency research − Reference is made in the Draft Report to the FDA guidance known as the "Emergency Medicine Exception from Informed Consent", which allows the exception from consent for clinical investigations in emergency research, and the possible biases from withdrawal of consent. However, none of the rFVIIa clinical trials has been conducted using this FDA provision.	The report more clearly acknowledges that the two Boffard, et al. clinical trials of rFVIIa use in trauma were organized outside of the U.S. and included only non-U.S. centers (pages 97-98). Based on the published description of the trials' methods (included together in one article), the trials appear to have used some form of waiver of consent, along with concurrent allowance for participants to withdraw consent. The following statement is included in the "methods" section of the Boffard article that reports the results of these trials (sponsored by the manufacturer): "Informed consent was obtained from all patients or, where applicable, from the legally authorized representatives. Because of the emergency conditions and the possible absence of relatives at enrollment into the trial, waived informed consent was authorized by the ethics committees. However, whenever a patient was included without written informed consent, such consent was promptly sought from the legally authorized representative and subsequently from the patient. Adequate confirmation of consent was not obtained for six patients, and their data were excluded from analysis." (Boffard KD, Riou B, Warren B, et al. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. J Trauma. 2005;59(1):8-15; discussion 15-18.)
Results	• Publication bias − The statement in the Draft Report that the results of the cardiac surgery trial have "yet to be published either in abstract form or as an article " is incorrect. Although the full manuscript describing the results of the study was not published at the time this Draft Report was written, an abstract and a full manuscript have since been published in	The report includes in all relevant primary analyses (pages 137-138 and Figures 21-24) the published cardiac surgery RCT in Circulation, which had previously been included in our sensitivity analyses when partial information from the manufacturer's website was the only information available.

	Circulation.(refs 1,2) The delay in manuscript publication arose precisely because the sponsor (Novo Nordisk) did not seek to influence the independent decision-making of the clinical investigators, who opted to submit the manuscript to a journal with an exceptionally high rejection rate, resulting in a delay in publication.	
Results	• Effects of confounding factors on efficacy − Conclusions regarding the benefits or lack thereof from the use of rFVIIa are drawn in situations with potential confounding factors, such as those in which there are survival benefits of treatment.	The Report notes the difficulty of interpretation of study findings and issues of confounding (particularly in observational studies) within the discussion of each of the respective indications. For example, the Key Question on intracranial hemorrhage contains a sub-section devoted to the discussion of the timing of rFVIIa dosing and outcomes ("Other Considerations: Timing of rFVIIa and Changes in ICH volume," page 75).
Results	• Unpublished studies − The two large, randomized controlled trials on the efficacy and safety of rFVIIa in cardiac surgery and trauma were not published at the time this Draft Report was written. The potential effects of these two studies on the evaluations presented in this review should be noted.	The report has been updated through August 4, 2009. The report still does not include full information on the multi-center CONTROL trauma trial, the only available information is partial from the manufacturer's website (Evaluation of Recombinant Factor VIIa in Patients With Severe Bleeding Due to Trauma. Clinicaltrials.gov identifier: NCT00323570.), an abstract (Massive blood loss: does rFVIIa help? Paper presented at: International symposium of intensive care and medicine; March 24-27, 2009 Brussels, Belgium. http://www.intensive.org/newsletter/fullday2.html (Accessed 11-5-09)), and a commentary of the problems faced by the trial (Dutton R, Hauser C, Boffard K, et al. Scientific and logistical challenges in designing the CONTROL trial: recombinant factor VIIa in severe trauma patients with refractory bleeding. Clin Trials. 2009;6(5):467-479.). The contents of this information suggest that the main findings of the report for trauma will not be altered by full publication of that RCT. In addition, as discussed further below, other trials not yet published in full, but which report on information relevant to our findings, were also monitored. Through this examination of the grey literature (e.g., postings on ClinicalTrials.gov and the manufacturer's website and abstracts without subsequent full publications) it is clear that some RCTs have been concluded (or are soon to be concluded), but are not yet published. The nature of an evidence report is such that we can only incorporate data found in the public domain.
Results	It is unclear from the Draft Report how the estimates for the 6,000 acute care hospitals in the United States were extrapolated from the 615 hospital sample in the Premier database. There is also no	Premier, Inc. produces its dataset as a means of providing data on national patterns of hospital use. For proprietary reasons, Premier does not share their specific sampling methodology,

	comparison of the type of hospitals and geographic locations to national estimates. While there are only 140 federally funded HTCs, the proportion of HTC-affiliated hospitals in the Premier sample is not stated. Any over- or under-representation of HTC-affiliated hospitals, with their significantly higher rate of encountering hemophilia patients, would introduce enormous distortions into the extrapolations, yet no account seems to have been made of this possibility. Apart from data implying a multiplication factor of approximately 5.83, there is no information as to whether the estimates are derived from a multi-factorial comparison of the total Premier dataset captured for each diagnosis or procedure to the national estimates, with consideration for location and hospital types, or whether this is done in aggregate across all estimates.	but it claims that its database provides nationally representative estimates. There is no reason to suspect that there is systematic bias in how the sample is constructed. Data from Premier has been used in other published analyses of hospital practices, including analysis of rFVIIa use. (O'Connell KA, Wood JJ, Wise RP, Lozier JN, Braun MM. Thromboembolic adverse events after use of recombinant human coagulation factor VIIa. Jama. 2006;295(3):293-298.) Access was obtained only for those data pertaining to hospital cases where rFVIIa had been dispensed. Therefore, it was not possible to produce information on the number of total cases by procedure or diagnosis regardless of whether rFVIIa had been used. This latter point is stated in the Methods section of the report (page 42).
Results	Taking all these issues into consideration, the statements in the Abstract, Summary and Results of the Draft Report that "rFVIIa use in the U.S. has increased 70-fold since 2000 solely due to rising off-label use" and constitutes "97%" of sales are clearly inaccurate. Further, using the term "70-fold increase" from the time of product launch in 1999 serves only to confuse the reader, when the baseline from which such multiples are said to have grown is zero or very close to it. Although the Draft Report acknowledges the exclusion of outpatient on-label use, it is not until page 146 that this appears. We believe that this acknowledgment belongs in the Abstract and Executive Summary of the AHRQ Draft Report.	The report includes further clarification that the data analysis pertains to in-hospital use of rFVIIa within the abstract, executive summary and main text of the report. The report notes that a majority of rFVIIa use occurs in outpatient settings and that a majority of outpatient use is related to the FDA-approved indication of hemophilia. Presentation of data restricted to the hospital setting is valuable because this appears to be a leading area where off-label use is dominant, and the Key Questions for the report focus on off-label use.
Results	1.32 Waiver of consent for clinical investigations in emergency research Reference is made in the Draft Report to the FDA guidance known as the "Emergency Medicine Exception From Informed Consent", which allows exception from consent for clinical investigations in emergency research, and the possible biases from withdrawal of consent. However, this subject is not germane to the use of rFVIIa in clinical trials, as none of the rFVIIa clinical trials has been conducted using this FDA provision. All patients enrolled had to have prior consent according to US regulations, and the methods for obtaining prior consent depended on the local regulations. In the United States, the patient or their legally authorized representative had to provide consent for inclusion in a clinical study, and outside the US, either the patient or legal representative, or separate consents from two physicians were used where permitted by local ethics regulations (particularly in ICH-137120). Subjects were able to withdraw consent from further trial activities when they regained their functionality. Therefore, the statements on the use of the FDA exception rule in	As described above, the report more clearly acknowledges that the two Boffard, et al. clinical trials of rFVIIa use in trauma were organized outside of the U.S. and included only non-U.S. centers (pages 97-98). Based on the published description (included in one article) of the trials' methods, the trials appear to have used some form of waiver of consent, along with concurrent allowance for participants to withdraw consent. The following statement is included in the "methods" section of the Boffard article that reports the results of these trials (sponsored by the manufacturer): "Informed consent was obtained from all patients or, where applicable, from the legally authorized representatives. Because of the emergency conditions and the possible absence of relatives at enrollment into the trial, waived informed consent was authorized by the ethics committees. However, whenever a patient was included without written informed consent, such consent was promptly sought from the

	reference to rFVIIa trials should be removed.	legally authorized representative and subsequently from the patient. Adequate confirmation of consent was not obtained for six patients, and their data were excluded from analysis." (Boffard KD, Riou B, Warren B, et al. Recombinant factor VIIa as adjunctive therapy for bleeding control in severely injured trauma patients: two parallel randomized, placebo-controlled, double-blind clinical trials. J Trauma. 2005;59(1):8-15; discussion 15-18.)
Results	13.3 Publication bias The statement on page 170 of the Draft Report that the results of the cardiac surgery trial have "yet to be published either in abstract form or as an article" is incorrect. In particular, the implication that there was an element of intentional delay of publication of the results of this trial is incorrect and unfortunate. The manuscript describing the results of this study was not published at the time this Draft Report was written, but has now been published in Circulation. 1 We would also point out that in addition to the published manuscript, the results of the study were presented to the steering committee members in January 2008, within weeks of the close of the study, then to the study investigators in April 2008. It was also presented at an NCME Symposium in June 2008 and at the Annual Scientific Meeting of the American Heart Association in November 2008, from which an abstract was published in viii C2irculation The delay in manuscript publication arose precisely because the sponsor (Novo Nordisk) did not seek to influence the independent decision-making of the clinical investigators. Against the advice of the sponsor, the external authors of the manuscript opted to submit it to a journal with an exceptionally high rejection rate. This initial submission occurred in the second quarter of 2008 and the subsequent rejection by that journal resulted in a 6-month delay in publication.	As noted above, the literature review has been updated through August 4, 2009. We have included the cited cardiac surgery trial study in our results. Complete information on the CONTROL trauma trial is still lacking, but exists as an abstract (Massive blood loss: does rFVIIa help? Paper presented at: International symposium of intensive care and medicine; March 24-27, 2009 Brussels, Belgium. http://www.intensive.org/newsletter/fullday2.html (Accessed 11-5-09), a commentary on the problems encountered in the trial (Dutton R, Hauser C, Boffard K, et al. Scientific and logistical challenges in designing the CONTROL trial: recombinant factor VIIa in severe trauma patients with refractory bleeding. Clin Trials. 2009;6(5):467-479.), and information obtained from the manufacturer's website [Novo Nordisk. http://www.novonordisk-trials.com/WebSite/search/trial-result-details.aspx?id=1414. Accessed: May 22, 2009.; Novo Nordisk. Synopsis: A multi-centre, randomised, double-blind, placebo-controlled, dose escalation trial on safety and efficacy of activated recombinant factor VII (rFVIIa/NovoSeven®) in the treatment of post-operative bleeding in patients following cardiac surgery requiring cardiopulmonary bypass. Available at: http://www.novonordisk-trials.com/website/pdf/registry/bin_20081120-011014-384.pdf. Accessed: November 13, 2009]. The incomplete information obtained from these sources nonetheless suggests that the main findings of the report for trauma will not be altered by any additional information. In addition, as discussed further below, we have monitored the grey literature for any other trials not yet published in full, and report our findings. Through our examination of the grey literature (e.g., postings on ClinicalTrials.gov and manufacturer's website and abstracts without subsequent full publications) it is clear that some RCTs have been concluded (or are soon to be concluded), but are not yet published. The nature of an evidence report is such that it can only incorporate data found in the public domain.

Results	22 Intracranial hemorrhage The two dose-escalation non-parallel safety studies (Mayer 2005b31 and Mayer 200632) are inappropriately combined with the Phase 2 and Phase 3 randomized, parallel-arm, efficacy studies (Mayer 2005a2° and Mayer 200821) in the evaluation of efficacy in the Draft Report. The intent of these dose-escalation studies was to determine the maximal safe doses or dose ranges for subsequent study in parallelarm assessments; hence, they were not powered for the evaluation of efficacy. More importantly, the rFVIIa doses used in these studies were later demonstrated to be ineffective in limiting hemorrhage. The heterogeneity and disparity in sample size among the four studies further restricts pooling of data from these studies for meta analysis. Therefore, the validity of these evaluations is questioned. Further, the sample sizes for the Mayer 2005a study are incorrectly reported as 495 total subjects (page 53 of the Draft Report) and as 399 rFVIIa-treated subjects (Table 17). The correct sampie sizes are 303 rFVIIa-treated and 96 placebo-treated subjects, giving a total of 399 subjects. “Poor outcome” on the modified Rankin Scale Score was defined as mRS of 4-6 for ICH-1371 (Reference 21)20 and due to regulatory considerations was defined as 5-6 for ICH-1641 (Reference 75)21. We recommend that these definitions of “poor outcome” be notated on Table 18 and Figure 8 of the Draft Report. Further, as the definitions for poor outcome on mRS are different, it is inappropriate to pool these studies for the meta-analysis shown in Figure 8, as it misrepresents the data. The Draft Report recognizes early on the relationship between hemorrhage size and outcome (Brott 199717 and Davis 200618), but subsequently places little value on the relationship between hematoma expansion and outcome (see page 67, Table 23). Importantly, the clear dose effects demonstrated for ICH-1371 and ICH-1641 are paid little attention (See Table 20). Also notably absent is a study on the determinants of hemorrhage growth and a recent post-hoc analysis of the ICH-1641 published in Stroke.’6’22	Study sample size in and of itself should not restrict pooling, which is a notable strength of meta-analyses. See the above comments regarding pooling of ICH studies with different rFVIIa doses. The reviewer comment above does not provide references for their statements regarding “the rFVIIa doses used in these [smaller] studies were later demonstrated to be ineffective in limiting hemorrhage,” so it is difficult to respond to this comment. We have corrected the sample size errors regarding “495” in the text and “399” in the table. The report continues to note the statistically significant findings based on meta-analysis of rFVIIa impact on reduction of hematoma expansion (a surrogate outcome), but also states that there was no evidence of reduction in measures of direct outcomes (mortality and poor functional outcome as measured on the modified Rankin scale score). The footnote to the referenced table continues to contain the following explanation regarding the modified Rankin score: “Poor outcome defined as modified Rankin Scale (mRS) score of 4-6. Data for mRS scores of 4-6 in Mayer NEJM 2008[88] were derived graphically from figure 3 in the paper....” (page 82) This is also noted in the “qualitative discussion of heterogeneity” section (page 72). The reviewer does not provide the full reference for the post-hoc analyses mentioned, so a response to this is not possible, as it is not certain what article is referenced. The report continues to contain a section discussing various post hoc analyses in the “other considerations” section for the intracranial hemorrhage indication (page 75).
Results	2.3 Trauma The reports from military and civilian trauma populations should not be pooled because the wound patterns in the two settings are vastly different. Examining the studies individually yields a very different conclusion regarding the strength of the evidence. As an illustration, the Spinella33 and Rizoli34 reports represent military and x civilian populations, respectively. Evaluated on its own, the 30-day mortality in the Spinella study is significantly different at the p=0.002 level; therefore, it follows that the 30-day mortality precision of this study should be revised to “precise”. Further, Spinella does not “weakly” favor rFVIIa, rather it should be classified as “favoring” rFVIIa.	The report includes a discussion of the decisions regarding heterogeneity in the section “qualitative consideration of heterogeneity” for the body trauma studies that states, “The RCTs and observational trials included both blunt and penetrating mechanisms and were from both civilian and military populations. Different anatomic mechanisms of injury often result in the final common pathways of severe tissue injury and hypotension, and these conditions are thought to drive the coagulopathy of trauma. Therefore, despite the differences in injury mechanisms, injuries of sufficient severity

	It follows then that the overall strength of the Spinella study regarding 30- day mortality is not "low" but "moderate". "Low" implies that repetition will not necessarily produce the same results. Given the robust p value of 0.002, the definition of "moderate" given on page 19 of the Draft Report more closely applies, although further research may change the estimate. The dose-escalation safety study TBI-1600 (Narayan 2008) is inappropriately used in the efficacy analyses. The intent of this study was to determine the maximal safe dose ranges for subsequent study in parallel-arm assessments; hence, it was not powered for efficacy assessments and included doses ranging from as low as 40 mcg/kg to 200 mcg/kg. In studies where there was a survival benefit of treatment, no conclusion regarding favoring or not-favoring red blood cell (RBC) transfusion should be made due to this confounding factor. To illustrate this point, RBC transfusion requirement is classified as "favoring usual care" in the Spinella study. This is misleading, since far more patients treated with rFVIIa were alive at 30 days and thus were available to receive blood as a result of their lower mortality rate (31% rFVIIa versus 51% usual care). Since this was the case, treatment would favor rFVIIa and the increased administration of RBCs was a manifestation of the survival benefit of rFVIIa treatment. The "Applicability" paragraph indicates that the inclusion of patients with isolated traumatic brain injury (TBI) is a limitation, since many patients often present with polytrauma. This is an unwarranted criticism. First, patients with isolated T8I are a well-defined group that commonly confronts trauma surgeons and about whom information is clearly needed. Second, although polytrauma patients are seen, the most common scenario is polytrauma in the setting of TBI, in which the severity of the head injury trumps that of other injuries and where the other injuries are not of a life-threatening hemorrhagic nature. Therefore, this sentence should be removed.	do share physiologic characteristics. The role of FVIIa is to act upon these physiologic disturbances. For this reason, despite the heterogeneic mechanisms, we felt it appropriate to assess the patient populations together in this analysis." This explains the decision to evaluate together studies conducted in military and civilian populations. The report does not claim that the Stein TBI RCT was powered for efficacy outcomes. The word "limited" in the applicability section on brain trauma refers to how the composition of the dataset was restricted or limited: "…the data we evaluated from the Stein cohort was limited, in our analysis, by the inclusion of only those patients with isolated TBI."
Results	The data in Figure 12 appear to be incorrect. The figure reflects the increasing use of rFVIIa in pediatric surgery. If this is the case, the Premier database is suspect, since this does not comport with current usage patterns indicated by our data and patient models.	This figure (Figure 20, page 139) shows a flat line for the years 2006-2008 for pediatric cardiac surgery (i.e, no increase in use over those years), so it is not clear what this comment refers to. The report authors do not have access to the manufacturer's data.
Discussion	In future research, the authors indicate (as an example) that there were 5 RCTs in liver disease, but because the patient groups were not liver transplantation, they were not included in this AHRQ appraisal – but this seems almost dismissive of potentially important information. Additional information about these trials might be considered	We agree that rFVIIa use in liver disease in cirrhotic patients but outside of transplantation would be a fruitful area for future inquiry (see Future Research section under "Evidence Gaps", page 193). In particular, this may be an area of growing outpatient use of rFVIIa that we have not captured in our analysis of hospital data (where we note that use in liver disease is modest, page 61), given that we did identify three

		comparative studies on the topic (page 63 and Table 17), including one on use during liver biopsy procedures, which may be performed in the outpatient setting. Because we analyzed only in-hospital rFVIIa use, we may have underestimated the prominence of this off-label use. The analysis of this topic is beyond the scope of this report.
Discussion	The conclusions typically indicate 'rFVIIa provides limited benefits on surrogate outcomes' but this presumes that all relevant surrogate outcomes have been evaluated. This finding may also be not that unexpected given the approach of evaluating studies by selected clinical settings which include intracranial, trauma, liver transplantation, cardiac surgery and prostatectomy, some of which will inevitably only have smaller numbers of relevant trials for appraisal and evaluation.	We have clarified the relevant statements to indicate that they are limited to the surrogate outcomes reported in the studies: for example, in the Discussion section, "off-label rFVIIa may provide some benefit for certain clinical indications, but this conclusion is largely based on indirect outcomes that have an uncertain relationship to patient survival or functional status. (page 184)
Discussion	p174 Limitations of systematic review. Implausibly short. As indicated non-English language studies haven't been considered. No review yet has completely excluded the possibility missing unpublished literature, and this review is no exception - conference abstracts for one are unlikely to have been completely ascertained. The challenge is even greater for this review where observational studies are included. Excluding selective reporting of outcomes is also extremely difficult to achieve. Finally there is no mention of following up incomplete data in trial reports, which ideally all reviews would like to undertake.	We have included a more complete discussion of past systematic reviews (as described above, in our response to this same reviewer) and clarified in both the Methods and Results that foreign language articles were included in a narrative fashion, when an English-language abstract was available and as appropriate (page 48 and 187). The review of conference abstracts has been extensive, although missing important abstracts from non-U.S. and non-European conference is possible. With the help of several research librarians, an extensive search of the grey literature (including conference abstracts and online databases) was conducted (as described on page 33), but, again, there remains a potential for unreported data. We address all of the limitations cited by the reviewer in greater detail in the Discussion under the section "Limitations of the Systematic Review"
Discussion	Context p172. More could have been made of the complimentary nature of the approaches taken by other systematic reviews. The report reasonably considers evidence specific to clinical problems, and is a strength. However, whilst maximising applicability, this may sacrifice power in considering outcomes like adverse events which may as reasonably examined across indications. In relative terms it seems that changes in thromboembolic events, if increased, are likely to be consistently changed irrespective of the indication for which rFVIIa is being given. Reflecting on systematic reviews which have examined the data in this way may help strengthen your conclusions. In this respect we note that the Cochrane review has recently been up-dated and its publication is imminent. In addition, considering the larger number of included studies across all indications may also help make	While we do not disagree with the concept that certain adverse events "may reasonably be examined across indication," the report takes a cautious and clinically-oriented approach to this issue. For example, there are reasons to believe that certain patient populations (e.g., older patients and those with other reasons for increased thromboembolic risk—patient populations more common to ICH and adult cardiac surgery indications) might respond differently to rFVIIa in terms of risk for thromboembolic events. For these reason, the report continues to rely on indication-specific analyses despite the potential loss of statistical power associated with this approach. As noted above, we acknowledge that selection of the appropriate degree of specificity is difficult and may be controversial. Also as noted above, we have included more

	more definitive statements about issues like publication bias, too.	discussion of the findings of previous systematic reviews, including the results of the updated Cochrane review that considered multiple indications simultaneously.
Discussion	The report was a very nice summation of the data and the state of the literature. Aside from a few recent papers, I thought the literature included was appropriate. I would have concluded that FVIIa is a powerful procoagulant (otherwise how can it cause complications?) that may have a role in the treatment of coagulopathic hemorrhage. Assessment of potential risks and benefits in each individual case is important. Future research will be important in areas such as TBI, post pump hemorrhage, and reversal of therapeutic anticoagulation, but will be difficult to do at a high level of evidence because of the emergent nature of these conditions and the difficulties of conducting prospective randomized trials with sufficient power.	Regarding recently available papers, we have included the recently published multi-center trial of rFVIIa use in cardiovascular surgery (Gill R, Herbertson M, Vuylsteke A, et al. Safety and efficacy of recombinant activated factor VII: a randomized placebo-controlled trial in the setting of bleeding after cardiac surgery. Circulation. 2009;120(1):21-27) and further information about the yet to be published multi-center CONTROL trauma trial (Evaluation of Recombinant Factor VIIa in Patients With Severe Bleeding Due to Trauma. Clinicaltrials.gov identifier: NCT00323570.). We emphasize the mismatch between available evidence and current patterns of use. The inherent difficulties in studying end-stage and emergent use of rFVIIa contribute to this mismatch.
Conclusions	The prominent positioning of incorrect and misleading statements in the Abstract and in the Executive Summary is most unfortunate. The Draft Report starts from an erroneous presumption that virtually all uses of rFVIIa are for off-label indications. The generally careful analyses of off-label indications included in the Draft Report state that no useful conclusions can be drawn regarding the risks or benefits of rFVIIa in virtually all situations. The Draft Report equates failure to achieve regulatory approval with failure to arrest hemorrhage. Thus, the reader is left to conclude that rFVIIa is used primarily in off-label indications and is not effective in stopping bleeding. Neither of these conclusions is supported by the available information.	The report clarifies in relevant sections and in the title that the analysis includes only in-hospital application of rFVIIa. The report also notes the overall context of rFVIIa use, particularly that a majority of use occurs in outpatient settings and that a majority of outpatient use is related to hemophilia, the primary FDA approved indication.
Conclusions	When faced with hemorrhage unresponsive to conventional therapies, physicians, in honoring their oath as practitioners, apply all measures required to avoid the twin traps of overtreatment and therapeutic nihilism. When a physician prescribes medication, he or she is always evaluating the critical balance between risk and benefit. Faced with using off-label therapeutics that are expensive and have the potential for side effects, such an evaluation is even more important. In the hospital setting, rFVIIa is prescribed and monitored by well-qualified and professional teams of physicians, pharmacists and other healthcare providers who typically work according to institutionally agreed protocols often based on peer-reviewed published guidelines. (refs 3,4) These are precisely the medical experts for whom guidance from AHRQ would be most beneficial. Any assessment of a drug class or specific agent must also take into consideration the decision roles of the very healthcare professionals who are best suited to balance	Consistent with these comments, the report assumes that practitioners can benefit from the systematic review of information in their approach to individual patient care decisions. In no way is this review expected to substitute for clinician expertise and knowledge in the care of individual patients. It is important that clinicians incorporate available evidence into their decisions and be aware of the lack of evidence supporting particular practices. The goal of this report is to inform physicians so that their practices reflect the state of evidence around rFVIIa. In particular, it is critical that physicians not equate the ability of rFVIIa to produce cessation of bleeding with improved patient outcomes. Although this presumption has a common sense appeal, current evidence does not support this conclusion.

	potential risks and benefits. As the Draft Report details in the systematic review of published studies, there is inadequate evidence to make broad regulatory-based decisions on efficacy. Any decision regarding risks and benefits must be driven by the unique conditions for a given patient. These decisions are best made at the bedside or in the operating arena by the responsible physician.	
Conclusions	1.L3 Failure to accurately assess denominator rFVIIa use. The conclusion in the Draft Report that the off-label use of rFVIIa is "common" is incorrect, since it does not establish the denominator of total discharges by diagnosis or procedure, and the estimated uses are infrequent when placed in the context of published estimates of the denominator. While some studies might hint towards an early intervention (e.g., in prophylaxis use) in high-risk patients (e.g., Diprose et al.11), the use patterns put in context do not support the characterization of widespread or "common use." There is evidence that off-label use of rFVIIa occurs primarily in high-risk patients in times of extremis.	The report no longer states that rFVIIa is common. Instead, the report refers to rFVIIa use as becoming "more frequent" over time with the intent of capturing the time trends of increasing or, for some indications, possible leveling off of in-hospital use.
Conclusions	Given the lack of hospital reimbursement for inpatient rFVIIa use apart from the normal diagnostic related group (DRG) payments outside hemophilia, it is unlikely that hospitals would have condoned increases in these types of rFVIIa usage.	Not all hospitalizations are reimbursed through a DRG payment and many Medicaid programs reimburse for rFVIIa use. Even under DRG payment systems (e.g., Medicare), hospitals have the ability to obtain additional reimbursement beyond their DRG payment for the use of special medications, including rFVIIa.
Conclusions	Many data sources can be used to estimate the number of cardiac surgeries (CABG and valve) annually in the United States. For example, the Society of Thoracic Surgeons, which maintains a national adult cardiac surgery database that represents tracking from 80% of hospitals performing cardiac surgeries, tracked 270,012 total procedures in 2008 (158,750 isolated CABG), yielding an estimate of some 330,000 total eligible procedures.12 Even using the liberal estimate provided in the Draft Report that dosing in cardiac surgery occurred in 5,250 events, this would extrapolate to less than 1.6% of cases. This does not seem consistent with the widely accepted use of the term "routine." A similar analysis can be done for other indications. The American Heart Association (AHA) estimates that the incidence of intracerebral hemorrhagic is 10% of the 795,000 stroke patients each year. About 20% of these are complicated by the concomitant use of warfarin. A liberal estimate from the Premier dataset would suggest that approximately 2,000 patients with ICH are treated annually. This constitutes less than 3% of all ICH discharges.	As above, the report does not have the ability to calculate or comment on the relative frequency of rFVIIa use among all hospital cases of the specific indications that were investigated. The report was limited to information on patients where rFVIIa had been dispensed. As noted above, the report no longer uses the term "routine" and instead has replaced it with the phrase "more frequent."
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General comments	I am not familiar with the terminology "arcsine summary effect" throughout the paper. It seems intuitively clear from the figures that the differences described by this method are meaningful, and have the stated benefit/lack of benefit in the text, but perhaps an explanation of this term would be appropriate for an audience of non-statisticians like myself.	We have included a better explanation of the arc sine statistic (in both the Executive Summary and Report), including its strengths (loses the least amount of statistical information) and weaknesses (it is less well known, see page 45 in the methods section of the main report). There are important technical advantages of this method, particularly where the outcomes of interest are rare and no events are observed in both arms of a trial. The arc sine method includes information from such trials while the risk difference method does not. The report contains both the risk difference (in the main report) and arc sine summary statistic (in the appendix). The results for both metrics show consistent findings.
General comments	Throughout the manuscript there is no need to capitalize terms such as "Factor X" or "Factor IX" or "Factor VIII" as if they were proper nouns, which they are not.	The Report has been modified to reflect this suggestion.
General comments	Ref 24 and 52 refer to the same Cochrane review	We have corrected this error.
General comments	The report was somewhat redundant, but maybe this was just my unfamiliarity with the requirements of this format. I am concerned about the clinical relevance because I believe that much of the off-label use of FVIIa in real life is last ditch rescue efforts in dying patients. In this population concern for complications is naturally down-played, while even the potential for benefit might justify use. This sort of usage also makes retrospective analysis difficult, because the patients in real life are often sicker than they would appear from usual risk adjustment	We have included a framework that distinguishes prophylactic use, treatment use, and end-stage use of rFVIIa and further emphasizes the difficulty of using data derived from studies of prophylactic and treatment use to gain clinical insights into the end-stage use of rFVIIa. We also discuss the type of use (prophylactic, treatment, and end-stage) within the context of our analytic framework for each indication.

	mechanisms. I don't believe these thoughts / limitations come across well in this draft report.	
General comments	Some areas deserve greater attention as mentioned below. Some figures difficult to interpret.	As noted above, we have included additional information within the forest plots to aid in their interpretation.
General comments	The manuscript is quite long and somewhat repetitive. It could be easily shortened.	The difference formats used are each required by the AHRQ report format. While there are some sections that cover similar topics within each key indication, these sections are needed so that the reporting of each key indication can stand on its own. To some degree, this reflects that information on each key indication is in some sense a separate report. When possible, we have sought to reduce the length of the report, particularly its Executive Summary.
General comments	The authors provide a huge amount of information with a lot of details -- apparently this is a huge amount of work. However, it may help the organization if the results are more structured around the questions of each key question, and there are many different types of comparison to Premier, and indications, etc. at different places	The report is structured to present findings for each key question. Although alternative strategies for organizing the report are possible, each key indication is described separately to maximize the extent to which each of these sections can be self-contained.
General comments	The report is not clinically meaningful because the conclusion is that we can draw no conclusions from the available data My comments are of a general nature. I was very impressed with the collection and compilation of data. This work is an excellent reference on the uses of rFVIIa. I am not qualified to comment on the statistical methods used to analyze the data. My main comment is related to the conclusions drawn from the reviewed studies. While I am inclined to agree that no firm conclusions can be drawn about most of the off-label uses of rFVIIa, I do think that a couple of points should be given more consideration. The authors have indeed noted that it is difficult to design a study to investigate the effects of a drug that is given "as a last resort" or for an indication for which there are few, if any, other therapeutic options. There is certainly little support for giving rFVIIa to any category of patients who are not bleeding excessively i.e. prophylactically. However, I think the data strongly suggest that rFVIIa does indeed have hemostatic effects in non-hemophilic patients. While the bulk of data do not support the conclusion that administration of rFVIIa increases survival of any group of patients, it still may be valuable when a specific patient continues to experience life-threatening hemorrhage in spite of conventional therapy (usually transfusion).	The report is indeed limited by the available evidence. The report is constrained in making definitive statements about the net benefits of rFVIIa. In addition, the report points out the mismatch that is present between available evidence and use of the drug as an end-stage therapy. As relevant, the report notes areas of clinical practice where rFVIIa may have the great likelihood of adding value, especially in the section on Future Research (page 193).
General comments	This is a very comprehensive and impressive report. It should be made widely available, not only to policy makers, but to caregivers who	We have more prominently emphasized the distinction between patient populations that are coagulopathic from oral

	use rFVIIa off label (like myself). As a brain hemorrhage specialist, my main comment is that I think there should be more differentiation between coagulopathic (OAT-related) and non-coagulopathic intracranial hemorrhage and the potential role of rFVIIa treatment. This goes for the executive summary as well as the body of the article. The distinction is important, because rFVIIa is well studied for non-coagulopathic ICH, but not for OAT-related bleeds rFVIIa might be much more effective for OAT-related bleeds OAT-related bleeds have a much higher mortality, progressive bleeding risk, and mortality rate Most off-label use of RFVIIa for intracranial bleeding is for OAT-related bleeds (with the negative results of the FAST trial, compassionate use of rVFIIa for non-coagulopathic ICH has essentially stopped). If this distinction is made more clearly, I think that the evidence would indicate that there is a very strong imperative to support research investigating rFVIIa for OAT-related intracranial hemorrhage, since (1) there is great promise with this approach, (2) this is where most of the off-label use is now, and (3) there is no high-quality data looking at this subset of patients.	anticoagulation therapy and those not on such therapy (page 71). The report also points to this more narrow population as an important target for future studies (page 194).
General comments	It is an excellent well written report. The issues are completely and accurately analyzed. It should provide interesting reading for many parties. Some of the results also set the stage for possible future studies (i.e., - the suggestion of a partial benefit of rFVIIa in blunt trauma). I have nothing further to add. I look forward to the formal publication.	We thank the reviewer for their comment.