Author's response to reviews

Title: Impact of Bleeding-related Complications and Blood Product Transfusions on Hospital Costs in Inpatient Surgical Patients

Authors:

Michael E Stokes (Michael.Stokes@UnitedBioSource.com)
Xin Ye (Sye2@ITS.JNJ.com)
Manan Shah (Manan.Shah@xcenda.com)
Katie Mercaldi (Katie.Mercaldi@UnitedBioSource.com)
Matthew W Reynolds (Matthew.Reynolds@UnitedBioSource.com)
Marcia FT Rupnow (MRupnow1@its.jnj.com)
Jeffrey Hammond (Jhammon2@its.jnj.com)

Version: 3 Date: 10 October 2010

Author's response to reviews: see over
October 11, 2010

Melissa Norton, MD, Editor-in-Chief
BMC Health Services Research
BioMed Central Ltd (publisher)
Floor 6, 236 Gray's Inn Road
London WC1X 8HL
United Kingdom
Editorial email: editorial@biomedcentral.com
Telephone: +44 (0)20 3192 2000
Facsimile: +44 (0)20 3192 2010

Re: Impact of Bleeding-related Complications and Blood Product Transfusions on Hospital Costs in Inpatient Surgical Patients

Dear Dr. Norton:

Please find attached our revised manuscript entitled “Impact of Bleeding-related Complications and Blood Product Transfusions on Hospital Costs in Inpatient Surgical Patients.” This letter provides point-by-point replies to each of the reviewers’ comments and how these have been addressed. In responding to some of the reviewers’ concerns we uncovered an error in the program used to analyze results for the reproductive organ cohort. This error has been corrected and we have updated the manuscript with the corrected values. Additionally, we have added results for an 8th surgical cohort (spinal surgery) to the manuscript which became available during the course of this revision.

Thank you for the opportunity to publish this article in the BMC Health Services Research online journal. We hope our responses to the reviewers’ comments and the changes made to our manuscript have adequately addressed the concerns regarding this study. If not, please do not hesitate to give me a call.

Sincerely,

Michael E. Stokes, MPH
MES:neb
Major Revisions

The authors need to address the following “Major Compulsory Revisions” –

1. In the materials and methods section of the manuscript, the authors mention that PCD database is the largest source of inpatient clinical, drug utilization, and cost based economic data in the US. Is the PCD database larger than the Nationwide Inpatient Sample (NIS) of the HCUP? The obvious benefit of using the PCD database is that it provides information on drug utilization which is lacking in the NIS data. However, I am not sure if the PCD is larger than the NIS database in terms of the sample size.

   The NIS contains data from approximately 8 million hospital stays each year.

   To avoid claims that are not true or misleading regarding the size of the database, we have deleted the sentence from the first paragraph of the Methods “This database is the largest source of inpatient clinical, drug utilization, and cost based economic data in the US.” The next sentence was also modified to read: “The current study used PCD data containing inpatient clinical, drug utilization, and cost based economic data for more than 600 hospitals in the US.”

2. Is the PCD data nationally representative? Are sample weights available to project the estimates to nationwide levels? It would be beneficial if the authors could elaborate more on these in the methods section.

   The Premier database contains hospital administrative data that includes approximately one sixth of all hospitalizations in the United States and it is nationally representative. We have added this point to the Data Source sub-section (first paragraph) of the Materials and Methods section:

   “The current study used PCD data containing inpatient, clinical, drug utilization, and hospital cost data for more than 600 hospitals throughout the US. Premier collects data from participating hospitals in its healthcare alliance. The Premier healthcare alliance was formed for hospitals to share knowledge, improve patient safety, and to reduce risks. The PCD is comprised of hospital administrative data which represents approximately one sixth of all hospitalizations in the United States and, although the PCD excludes federally-funded hospitals (e.g., Veterans Affairs), the hospitals included are nationally representative based on bed size, geographic location, and teaching hospital status [16].”

3. From the methods section, I get an impression that the unit of analysis was the individual discharge (patient level). The multivariate regression analysis for costs was conducted by using the ordinary least squares approach. How did the authors adjust for the effects of clustering of outcomes of patients within hospitals? This could have been a problem if bleeding complication patients were clustered within hospitals that had higher costs relative to those without complications.
This could have overstated the costs of bleeding related complications. Although, we did examine hospital characteristics among patients with a bleeding complication and those without a complication (Table 4). We did not conclude that there were meaningful differences in hospital characteristics between study groups. This provides support that the hospitals treating patients with bleeding complications probably did not have higher (or lower) costs versus hospitals treating patients without bleeding complications. We also ran multivariate cost analyses including hospital site as a covariate (and excluding the hospital characteristic variables) to see the effect on results. The incremental cost per hospitalization associated with bleeding-related complications estimated from multivariate analyses was similar to the main study results ($15,667 for vascular, $13,124 for solid organ, $13,790 for non-cardiac thoracic, $11,778 for cardiac, $4,798 for general, $2,430 for knee/hip replacement, $2,718 for reproductive organ, and $15,417 for spinal surgery).

Did the authors consider the possibility of using Generalized Estimating Equations methods to adjust for the same? Based on above, we did not feel that using a GEE approach would have significantly changed our results that much. If reviewers feel that running analyses using a GEE approach is necessary, we can do so with the next revision.

4. Several co-morbid conditions were included in the multivariate regression analysis. What was the rationale behind including these conditions in the multivariate model? It would be helpful if the authors mention about this in the methods section.

We included comorbidities that could have had an influence on total hospital costs. For example, patients with cancer probably would have had higher hospital costs versus those without cancer. If there was an imbalance in cancer cases across study groups, this could have biased the incremental difference in costs between patients with a bleeding complication and those without a bleeding complication. In the 6th paragraph of the methods we state that:

“Baseline parameters, clinical characteristics, and comorbid conditions deemed to have an impact on total hospital costs were considered for inclusion into multivariate models.”

Because we relied on administrative codes to identify comorbid conditions, we were not able to distinguish comorbid conditions occurring as post-op complications from those present pre-operatively. As this could have had an effect on parameter estimates, variability, and p-values of the multivariate analyses, we re-ran multivariate analyses with only the conditions that we could reliably distinguish as being present pre-operatively. These included diabetes, obesity, COPD, cancer, and liver cirrhosis.

The 9th paragraph of the Discussion was modified as follows to address this issue:

“…Because data on outpatient physician visits are not included in the PCD, for some comorbidities including thrombocytopenia, MI, hypertension, non-MI coronary disease, renal disease, congestive heart failure, and deep vein thrombosis it was impossible to determine whether the condition was chronic and unrelated to the index surgical hospitalization or occurred
as an adverse event related to the surgery or bleeding complication. Therefore, the assumption of independence between covariates in our multivariate analyses may have been violated if, for example, certain conditions such as MI or renal failure developed as a result of the bleeding complication and were not actually pre-existing conditions. As a result regression models could have produced inaccurate estimates of regression coefficients, variability, and $P$-values. Therefore, multivariate cost analyses were also run using only the conditions that were deemed to be obvious chronic conditions identifiable in the database for patients $\geq 18$ years of age. These conditions included diabetes, obesity, COPD, cancer, and liver cirrhosis. The incremental cost per hospitalization associated with bleeding-related complications was similar to the main study results ($15,931$ for vascular, $15,410$ for solid organ, $14,653$ for non-cardiac thoracic, $11,715$ for cardiac, $5,114$ for general, $3,119$ for knee/hip replacement, $2,961$ for reproductive organ, and $17,707$ for spinal surgery) and the difference in costs among patients with bleeding-related complications and those without complications was statistically significant for every surgical cohort ($P<0.001$).”

5. The authors mention that length of stay in hospital and in the intensive care unit are outcome variables along with hospital costs. How was the length of stay distributed in this data?

We have added the following statistics to table 4 to show how hospital LOS was distributed:

<table>
<thead>
<tr>
<th>Hospital length of stay</th>
<th>Complication</th>
<th>No Complication</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean (SD)</td>
<td>10.5 (13.7)</td>
<td>4.5 (5.5)</td>
</tr>
<tr>
<td>Median (Range)</td>
<td>6.0 (1-615)</td>
<td>3 (1-495)</td>
</tr>
</tbody>
</table>

From these statistics, we can see from the data that there are clearly some high value observations that drive mean values upward. So, the data are not normally distributed. Although conventional statistical guidelines state that the t-test is strictly valid only if the cost data are normally distributed, these methods are known to be fairly robust to non-normality, especially if the sample size is large (see below reference).

Thompson SG and Barber JA. How should cost data in pragmatic randomised trials be analysed? BMJ Volume 320 29 April 2000

Why was a regression analysis not performed for identifying factors associated with length of stay?

The main purpose of this study was to estimate the economic burden associated with bleeding-related complications, so that is why a regression analysis was not performed for LOS. Also hospital LOS is one of the main drivers of cost in analyses of this type. Although, if the journal editors would express interest in such an analysis and can confirm that there is space available in the manuscript, we would be willing to incorporate these analyses into the paper.

6. Are the statistically significant number presented in Table 4 clinically
meaningful? Considering the huge sample of the database, it is not too surprising that some numbers were statistically significant.

Yes, we are in agreement with your statement. Please note that in the Results, 4th paragraph we state:

“Table 4 reports the characteristics of the hospital in which the surgery occurred. There were no relevant differences in hospital size, hospital location (urban vs. rural), or the proportion of patients treated in a teaching hospital across study groups. However, differences were statistically significant due to large sample sizes. The authors conclude that these differences were unimportant.”

7. The authors mention in the discussion section that certain covariates not included in the analysis (because of lack of their availability in the database) could influence costs. It would be helpful if the authors discuss in more detail about the possible covariates that could influence costs.

We have provided examples of the types of covariates that were not available in the Perspective database which could have influenced total costs in the 9th paragraph of the discussion:

“…we could not control for certain covariates known to affect costs because this information was not available in the PCD. These covariates included sociodemographic parameters such as smoking status and whether the patient was living alone. Although we identified patients who were obese using ICD-9-CM diagnosis codes (278.00-278.02), to the best of our knowledge it is unknown to what extent these codes can be used to accurately identify individuals who are obese.”

8. While the effects of presence of co-morbid conditions were adjusted in the analysis, could the severity of the co-morbid condition influence outcomes? Is the severity information available in the database?

We have added the following two sentences to the end of the 9th paragraph of the discussion:

“Finally, information relating to the severity of the comorbid condition was not available. As severity could have an impact on hospital costs, the inability to control for condition severity is another limitation of these analyses.”

Minor Essential Revisions –

1. The title of the study starts with the term “Impact”. Does the current study actually examine the “Impact” or “Association” of bleeding related complications with the outcomes?

We have modified the title of this article to:
“Impact of bleeding-related complications and/or blood product transfusions on hospital costs in inpatient surgical patients.”

Since we examined a group with bleeding-related complications and/or blood product transfusions and compared costs to those without these events, we do believe we were able to measure the impact of having a “bleeding-related complication and/or blood product transfusion.”

Reviewer #2

This study of hospital costs associated with post-operative bleeding complications/interventions is generally well-written, addresses an important issue and provides useful and interesting new data. However, the analysis and presentation raise some (generally addressable) issues. Specific comments follow:

Under the journal’s review criteria, it would appear mandatory that a revised manuscript would, at a minimum, explicitly address or comment on the issues raised below. This does not necessarily require that the analysis be redone.

ABSTRACT:
Assuming this is true, Results here and in the text should clarify that incremental LOS differences were unadjusted for covariates, while incremental “cost” differences were adjusted for covariates,

We have made this clearer in the abstract by modifying the following sentence in the Results section of abstract:

“Overall, incremental LOS associated with bleeding-related complications or transfusions (unadjusted for covariates) was…”

Results Section, Paragraph 5 was also modified as follows:

“Data on hospitalization lengths of stay (data presented in days and unadjusted for covariates) are presented in Figure 1 by surgical cohort and complication status.”

TEXT:

Introduction:
1st paragraph (and elsewhere): For surgical patients who present with bleeding, transfusion, death or other outcomes from hemorrhage may represent a consequence of the underlying condition (e.g., vascular trauma, hemorrhagic stroke [not applicable to this study], ruptured aortic aneurysm) rather than a complication caused by the surgical intervention itself. The abstract and paper should make clear the degree to which the authors are distinguishing between these two phenomena.
We have revised the first sentence of the 3rd paragraph of the Introduction to make clear that this study sought to investigate bleeding-related complications that were a consequence of the patients' surgeries rather than underlying conditions.

“The purpose of this study was to estimate the economic burden associated with bleeding-related complications as a consequence of surgery in eight inpatient surgical cohorts, including cardiac, vascular, non-cardiac thoracic, solid organ, general surgery, knee/hip replacement, and reproductive organ surgery.”

Second sentence in Intro section of the abstract has been modified to make this point clearer:

“This study examines the incidence and costs of bleeding-related complications and blood product transfusions occurring as a consequence of surgery in various inpatient surgical cohorts.”

Conclusion section of the abstract has also been modified to make more clear what the objective of the study was:

“This study characterizes the increased hospital LOS and cost associated with bleeding-related complications and/or transfusions occurring as a consequence of surgery, and supports implementation of blood-conservation strategies.”

Materials and Methods:
1st paragraph: The authors should briefly describe the PCD (inclusion criteria for patient and provider populations, how hospitals are chosen, etc.). Is this a claims-based administrative database of ICD-9-CM diagnosis and procedure codes (with some limits on numbers of possible diagnosis vs procedure code fields), augmented by demographic data, a database with other additional lab or imaging test data, a database that captures electronic health record text, or something else? Criteria and data sources for variables such as race, geographic region, urban/rural status, etc. should be included and/or referenced. Presumably the PCD has encrypted patient identifiers that allow multiple admissions for individual patients or admissions of different patients to the same hospital to be linked. It would appear that this study was eligible for expedited IRB review with a waiver of requirements for informed consent. It is not clear that it was exempt from a requirement for any (expedited) IRB review at all.

We have revised the first paragraph of the Methods to address the above points as follows:

“Data for this retrospective cohort study were obtained from Premier’s Perspective™ Comparative Database (PCD) [15]. The current study used PCD data containing inpatient, clinical, drug utilization, and hospital billing data for more than 600 hospitals throughout the US. Premier collects data from participating hospitals in its healthcare alliance. The Premier healthcare alliance was formed for hospitals to share knowledge, improve patient safety, and to reduce risks. The PCD is comprised of hospital administrative data which represents approximately one sixth of all hospitalizations in the United States and, although the PCD
excludes federally-funded hospitals (e.g., Veterans Affairs), the hospitals included are nationally representative based on bed size, geographic location, and teaching hospital status [16]. The PCD contains a patient-level date-stamped log for all procedures, medications, laboratory, and diagnostic services rendered during the hospital stay for approximately 5 million hospital discharge records per year. Data elements include hospital and patient identifiers, primary and secondary ICD-9 diagnosis and procedure codes, length of hospital stay, admission type and source (ER, SNF, home), and primary payer. Also available are data elements for demographic and hospital characteristics, including age, race, geographic region of residence, hospital bed size, teaching hospital status, and hospital location (urban or rural). Patient and provider information contained within the PCD are de-identified making it fully compliant with the Health Insurance Portability and Accountability Act privacy regulations. Thus, institutional review board approval is not a requirement for obtaining a data license from Premier and gaining access to the PCD.”

2nd paragraph: The 1/106-12/31/07 date range refers to the date of the first (or only) relevant surgical procedure, rather than to the date of admission or the date of discharge for the index admission, right? It would appear that use of the most recent admission would capture re-admission to manage bleeding from a prior surgical admission, rather than the original admission itself. Please comment.

We chose the most recent hospitalization to maximize the pre-index study period available for assessing baseline clinical characteristics. We don’t believe that capturing readmissions to manage bleeding from a prior surgical admission would have been likely due to the way in which sample inclusion criteria were implemented. The criteria state (2nd paragraph of the Methods section) that “Procedures related to surgeries of interest were identified using ICD-9-CM procedure codes (Table 1)”. For example, in order for a patient in the cardiac surgery cohort to be included in the analysis they had to have had a procedure code for either an operation on a heart valve, a heart vessel, other operations on heart and pericardium, etc. These procedures likely would not have been used to manage bleeding from a prior surgical admission.

Also, would cases transferred from one hospital to another for surgical management of bleeding form a prior operation therefore be excluded entirely, or would the first or second hospital stay (but not both) be included? It would appear that each admission should be categorized by the single most relevant procedure (based on some specified criteria) and then counted just once in the analysis.

If a patient’s most recent hospitalization represented a transfer from another hospital, it would have been excluded entirely from the analysis. In creating the algorithm for this study, we did not believe it would have been feasible to follow transfer patients and include them in the analysis. The exclusion of these patients makes for a more conservative analysis as these “transferred” patients likely would have had higher costs.

Please see the 6th paragraph of the discussion, we have added the following to address this issue:
“Second, patients were excluded from analyses if they were transferred from another hospital or an unknown source to ensure that complete hospitalization data were available for every patient. We did not feel that we could reliably identify and link multiple hospitalizations for patients transferred to another hospital using the administration codes in the database. As these transferred patients probably had higher costs relative to the current sample of patients, the exclusion of these patients likely had the effect of underestimating the total inpatient episode of care. Furthermore, if more patients with a bleeding-related complication were transferred to other hospitals versus those without bleeding-related complications, the incremental difference in costs between these groups may in fact be larger than what is currently reported.”

How were patients with Medicare managed care classified? Medicare managed care patients would have been classified as Medicare patients.

This reviewer is unclear as to the meaning of the last sentence in this paragraph.

We have revised the last two sentences in the 2nd paragraph of the methods to make clearer:

“A minority of patients (5%) were included in >1 study subgroup because they were operated on in surgical sites spanning multiple surgical categories during the index hospitalization. For example, patients who had an operation on the vessels of their head and neck in addition to their heart valves would have been included in the separate Vascular and Cardiac cohort analyses, respectively.”

We are aware that patients having multiple major surgical procedures during a hospitalization is likely a driver of total hospital costs. This parameter was included in multivariate analyses of costs.

What was the age range for included patients? It would appear that the different spectra of ages, procedures and covariates seen in pediatric surgical cases would argue for separate analyses of such cases if they were included in the study at all.

We did not exclude patients from the analysis based on age. The age range has been included in the table 3 data. We have conducted sensitivity analyses to test the effect of excluding these patients on results b/c the types of procedures could have been very different from adult patients. In the 7th paragraph of the discussion, we discuss this issue and findings of the sensitivity analyses:

“Third, pediatric patients <18 years of age were included in analyses. Although age was included as a covariate in multivariate cost models, one could argue that, because pediatric patients likely underwent different procedures compared to adult patients, the exclusion of these patients from the study probably would have been warranted. Sensitivity analyses excluding pediatric patients were conducted to test the effect of this subgroup on main study results. Upon exclusion of pediatric patients, the incremental cost per hospitalization associated with bleeding-related complications estimated from multivariate analyses was similar to the main study results ($14,613 for vascular, $12,929 for solid organ, $12,656 for non-cardiac thoracic, $9,772 for
cardiac, $4,453 for general, $3,001 for knee/hip replacement, $2,735 for reproductive organ, and $16,484 for spinal surgery).“

3rd paragraph: Pursuant to a more complete description of the PCD, was capture of cases with relevant ICD-9-CM diagnosis and procedure codes based solely on claims data, on automated review of electronic medical health record text, or something else?

It was based on capture of cases with relevant ICD-9-CM diagnosis and procedure codes based on the hospital’s billing data.

Presumably this was not manual data abstraction from the medical record. Per above, it would appear important to note, if true, that this study classified patients on the basis of bleeding only occurring as a complication caused by the surgical intervention itself (ICD-9-CM Dx codes 998.11 and 998.12) rather bleeding occurring as a consequence of the underlying or presenting condition (e.g., vascular trauma, ruptured aortic aneurysm, GI bleeding, bleeding into a tumor) from that or transfusion. Unless there was a time stamp as well as a date stamp, knowing the date of transfusion would not necessarily distinguish pre-op from post-op transfusion on the date of surgery. Did the authors consider excluding vascular trauma, ruptured aortic aneurysm, GI bleeding, etc., from the study to facilitate excluding bleeding occurring as a consequence of the underlying or presenting condition?

While it was our purpose to try to identify bleeding events occurring as a consequence of surgery, we acknowledge that with the inclusion of blood product transfusions in our definition, some patients may have had a transfusion that was unrelated to a bleeding-complication. We have added the limitation identified above to the 5th paragraph of the Discussion section.

“Additionally, it was not possible to differentiate between transfusions occurring as a consequence of the surgery from transfusions that were the result of an underlying or presenting condition such as vascular trauma or ruptured aortic aneurysms if the transfusion occurred on the same day of the surgery as only data regarding the day of the transfusion were available. Therefore, it is possible that some patients within the bleeding-event and/or blood product transfusion group had a transfusion that did not occur as a consequence of the surgery and were misclassified.”

4th paragraph: How were costs captured? Is this a) billed charges; b) societal-perspective medical care costs based on actual re-imbursement (reflecting insurer payment with or without patient co-payment and/or deductibles) or standardized allowable (e.g. Medicare-allowable re-imbursement); c) estimated provider-perspective costs based on hospital-wide or procedure group-specific cost-to-charge ratios or on activity-based cost analysis; or d) something else?
Based upon our documentation from those who administer the Premier database, direct costs are the actual costs for treating the patient as they get itemized and recorded in the hospital accounting system for each treated patient. Thus, the perspective of the analysis is from the hospital’s perspective. None of the cost variables are tied to reimbursement or payments from health insurers.

The 4th paragraph of the Materials and Methods has been revised as follows to make this more clear:

“The outcomes measured in this study included the total length of stay (LOS) in days, the number of days spent in an intensive care unit (ICU), and total hospital costs. Total hospital costs were the actual treatment costs incurred by the hospital and were the sum of the hospital’s direct and overhead costs. Direct costs represented services that were used by the patient and included items such as physician costs, treatment costs, and food [16]. Direct costs are recorded in the hospital accounting system as they get itemized for each patient and represent the costs of providing care from the hospital’s perspective. Cost variables are not tied to reimbursement or payments from health insurers. Overhead costs were costs associated with the overall functioning of the hospital and included nursing, administrative, and management staffing costs, as well as electricity and the depreciation of medical equipment [16]. These costs are added to each patient record in the hospital accounting system as a standard cost according to the hospital department(s) providing care. Costs accrued during the 2006 study calendar year were standardized to 2007 $US using the medical care component of the Consumer Price Index.”

Costs of physician services are mentioned. These costs would generally be borne by the patient and/or insurer and not captured as hospital costs per se. Also, physician services (e.g., of surgeons, anesthesiologists, radiologists and others providing care to surgical inpatients) would generally be captured using CPT-4 procedure codes rather than by ICD-9-CM procedure codes. Estimation of the costs of such physician services would differ from that of hospital costs. Please comment.

For physicians who are not employed directly by the hospital and those that receive reimbursement for their services from insurers would not have been included in the hospital cost-data. The physician costs within the Premier database must have been only for physicians directly employed by the hospital. We have modified this paragraph to make more clear.

Were “costs” from other years converted to 2007 dollars using relevant ratios of the Producer Price Index, the Consumer Price Index or some other approach?

Yes, costs were converted to 2007 dollars using the ratios from the medical care component of the consumer price index. This has been specified in the 4th paragraph of the Methods (last sentence):

“Costs accrued during the 2006 study calendar year were standardized to 2007 $US using the medical care component of the Consumer Price Index”
5th paragraph: This reviewer is unclear as to the meaning of the 2nd sentence in this paragraph. It would appear that the analysis of resource use (days, costs as defined) associated with the presence or absence of bleeding complications/procedures is a cohort study, while the analysis of (pre-) existing risk factors associated with the presence or absence of bleeding complications/procedures is actually a (potentially nested) case-control study calling for separate analytical runs. Please comment.

We have deleted the second and fourth sentences in this paragraph as they are not essential to the description of data analyses and we would like to avoid further confusion. This is a retrospective cohort study, NOT a case-control study as we did not match cases (patients with bleeding-related complications) and controls (patients without complications). To avoid confusion, we have modified the first sentence of the first paragraph in the Methods as follows:

“Data for this retrospective cohort study were obtained from Premier’s Perspective™ Comparative Database (PCD)”

6th paragraph: Re-transformation of natural log-transformed costs from OLS models may be associated with bias, especially if heteroskedasticity was present. Regression models using maximum likelihood for the generalized Gamma distribution have been described as a better alternative. Was this approach considered?

We recognize that using Duan’s smearing estimate could produce misleading results if heteroskedasticity is present. Following the advice of a recent survey of multivariate methods which can be used to analyze skewed cost data (Mihaylova et al. 2010. Health Economics), we decided to examine the sensitivity of analyses to retransformation using subgroup-specific smearing factors which account for heteroskedasticity. Under this assumption, costs related to bleeds are actually much higher versus base case analyses. Please see the 8th paragraph of the discussion for our discussion of this point:

“Fourth, our analyses of costs were adjusted for differences in baseline clinical and demographic characteristics using multivariate ordinary least squares regression with Duan’s smearing back retransformation. The approach used for retransformation should be dependent upon the nature of the error term on the transformed scale (Mihaylova et al. 2010). Since the distribution of the error term is usually unknown, reliance on the assumption of normality or homoskedasticity can lead to inconsistent estimates (Mihaylova et al. 2010). Therefore, we also examined the sensitivity of results to retransformation using subgroup-specific smearing factors as proposed by Manning (Manning 1998). Using this alternate retransformation method, cost estimates for patients with bleeding-related complications remained statistically significantly higher versus those without complications. The incremental differences in mean total costs (bleeding-related complication – no complication) for each of the surgical subgroups were higher compared to the main study results (cardiac: $17,055, vascular: $25,795, non-cardiac thoracic: $30,963, solid organ: $25,153, general: $16,567, knee/hip replacement: $4,009, reproductive organ: $7,707, and spinal surgery: $21,326).”
How was “admitted surgical diagnosis” coded for inclusion in the model as constructed?

“Admitted surgical diagnosis” refers to whether the admission type was urgent, elective, or emergency, as provided in the PCD. We have made this more clear in the 6th paragraph of the Methods.

How far before the operative date did the authors look for “prior hospitalizations”? Truncation at some preoperative interval (e.g. 6 mos. or 1 year) would avoid bias if durations of patient or hospital inclusion in the PCD was related to variables of interest in this study).

We used a preoperative interval of 6 months; this has been clarified in the 6th paragraph of the Methods section.

Were hospitalizations for any related or unrelated cause included and how were they coded? How were prior admissions with direct transfers from other hospitals to the hospital or the index admission handled?

Any cause hospitalizations were selected. Patients with prior hospitalizations that were direct transfers to the index admission were excluded from analyses as described in paragraph 2 of the Methods section so there could not have been a prior hospitalization of this type.

Were all co-morbidities listed modeled as separate covariates? Comorbidities were modeled as separate covariates, we have specified this in the 6th paragraph of the Methods section.

Were coagulopathies, pre-op anemia or the use of drugs such as bone marrow suppressants, considered as possible covariates?

The ability to control for certain comorbid conditions was limited by the fact that for many patients data re: hospitalizations prior to the index surgical hospitalization were not available. Therefore, for many patients, comorbidities were identified within the index surgical hospitalization. We recognize that this as a major limitation of these analyses and have highlighted this in the 9th paragraph of the discussion. We have also included a sensitivity analysis where we only include comorbidities that we were sure were pre-existing conditions (also see 9th paragraph of the discussion). Results do not seem to be all that different from base case analyses.

We mention the possible consequences of not including the above covariates in the last paragraph of the discussion section:

“We also did not control for conditions such as coagulopathy, anemia, or the use of bone marrow suppressants. If a higher percentage of patients in the bleeding complication group had these prior conditions or procedures, our cost estimates related to bleeding complications may have
been overstated especially if a prior hospitalization for these conditions or procedures was associated with higher costs during the study index surgical hospitalization.”

How were co-morbid conditions occurring as post-op complications (e.g., MI or renal failure) distinguished from those present pre-operatively?

Because we relied on administrative codes to identify comorbid conditions, we were not able to distinguish comorbid conditions occurring as post-op complications from those present pre-operatively. As this could have had an effect on parameter estimates, variability, and p-values of the multivariate analyses, we re-ran multivariate analyses with only the conditions that we could reliably distinguish as being present pre-operatively. These included diabetes, obesity, COPD, cancer, and liver cirrhosis.

The 9th paragraph of the Discussion was modified as follows to address this issue:

“...Because data on outpatient physician visits are not included in the PCD, for some comorbidities including thrombocytopenia, MI, hypertension, non-MI coronary disease, renal disease, congestive heart failure, and deep vein thrombosis it was impossible to determine whether the condition was chronic and unrelated to the index surgical hospitalization or occurred as an adverse event related to the surgery or bleeding complication. Therefore, the assumption of independence between covariates in our multivariate analyses may have been violated if, for example, certain conditions such as MI or renal failure developed as a result of the bleeding complication and were not actually pre-existing conditions. As a result regression models could have produced inaccurate estimates of regression coefficients, variability, and P-values. Therefore, multivariate cost analyses were also run using only the conditions that were deemed to be obvious chronic conditions identifiable in the database. These conditions included diabetes, obesity, COPD, cancer, and liver cirrhosis. The incremental cost per hospitalization associated with bleeding-related complications was similar to the main study results ($15,931 for vascular, $15,410 for solid organ, $14,653 for non-cardiac thoracic, $11,715 for cardiac, $5,114 for general, $3,119 for knee/hip replacement, $2,961 for reproductive organ, and $17,707 for spinal surgery) and the difference in costs among patients with bleeding-related complications and those without complications was statistically significant for every surgical cohort (P<0.001). Finally, information relating to the severity of the comorbid condition was not available. As severity could have an impact on hospital costs, the inability to control for severity is another limitation of our analysis.”

Obesity (and smoking status) are potentially relevant covariates that are poorly captured by administrative data. Were existing algorithms (e.g., of Brixer and of Kahende, Fu or Mapel respectively) for trying to capture these risk factors using diagnosis data considered?

We did not use algorithms from any of these authors. An attempt was made to identify some of these studies and it didn’t seem like these authors used diagnosis codes to identify obesity and smoking status but rather information recorded either by clinicians or the patients themselves. We have added the following to the 9th paragraph of the discussion to highlight these issues:
“…we could not control for certain covariates known to affect costs because this information was not available in the PCD. These covariates included sociodemographic parameters such as smoking status and whether the patient was living alone. Although we identified patients who were obese using ICD-9-CM diagnosis codes (278.00-278.02), to the best of our knowledge it is unknown to what extent these codes can be used to accurately identify individuals who are obese.”

Did the authors consider propensity scoring as an approach to adjust for possible confounders of the comparison between cases with vs without bleeding complications/interventions in terms of resource use outcomes?

Yes, we did consider this approach. One of the most intuitive approaches in using propensity scoring (PS) is to match individuals from the two study groups on their PS. In implementing this, some individuals may have been lost since it is important to match on PS as closely as possible. If the relationship between the bleeding complication status and costs were different among the individuals who were dropped then we could be ignoring important exposure effects. Additionally, we did not see PS techniques as being a more advantageous approach relative to multivariate methods since the use of PS cannot control for unmeasured confounders. Furthermore, we thought the use of the traditional multivariate approach to be more preferable since the sample size was sufficiently large in the bleeding-related complication groups compared to the number of confounders examined.

Was hierarchical modeling using generalized estimating equations or other approaches considered as a way to adjust for clustering of cases within hospitals? If a given hospital had generally higher costs, and, as an independent issue, had more bleeding complications, then some of the cost difference attributable to bleeding would actually be due to the hospitals higher costs.

We did not consider hierarchical modeling using GEE as a way to adjust for clustering of cases within hospitals. Although, we did examine hospital characteristics among patients with a bleeding complication and those without a complication (Table 4). We did not conclude that there were meaningful differences in hospital characteristics between study groups. This provides support that the hospitals treating patients with bleeding complications probably did not have higher (or lower) costs versus hospitals treating patients without bleeding complications. We also ran multivariate cost analyses including hospital site as a covariate (and excluding the hospital characteristic variables) to see the effect on results. The incremental cost per hospitalization associated with bleeding-related complications estimated from multivariate analyses was similar to the main study results ($15,667 for vascular, $13,124 for solid organ, $13,790 for non-cardiac thoracic, $11,778 for cardiac, $4,798 for general, $2,430 for knee/hip replacement, $2,718 for reproductive organ, and $15,417 for spinal surgery).

Results
2nd paragraph: It would help to clarify that “differences in baseline demographic and clinical measures were highly STATISTICALLY significant across study groups due to the large sample size” Please comment here and/or elsewhere on differences that the authors interpreted as important vs unimportant.
We have modified results paragraphs 2 and 3 to better highlight the differences in patient characteristics that the authors interpreted as being important as follows:

“Baseline demographic and clinical characteristics are presented in Table 3 according to bleeding-related complication and/or blood product transfusion status. All differences in baseline demographic and clinical measures were highly significant across study groups due to the large sample size. All differences that the authors interpreted as important are highlighted in the section below.

The authors interpreted differences between groups in study characteristics including age, gender, primary payer, having a prior surgery as well as comorbidities including diabetes, COPD, and cancer to be important. Patients who had a bleeding-related complication were on average 9.0 years older compared to patients without a complication (mean age 64.3 years vs. 55.3, P<0.001). There were relevant differences across study groups with respect to the patients’ primary payer of medical care. There was a higher percentage of patients experiencing a bleeding-related complication and/or blood product transfusion who received Medicare reimbursement versus patients without these events (58.3% vs. 38.7%, P<0.001). A higher percentage of male patients had a bleeding-related complication versus those without a complication (45.9% vs. 35.9%, P<0.001). Patients with bleeding-related complications and/or blood product transfusions were more likely to have diabetes (47.0% vs. 26.8%, P<0.001), COPD (25.5% vs. 19.0%, P<0.001), and cancer (23.5% vs. 17.8%, P<0.001) compared to those without these events. We interpreted statistically significant differences with respect to demographic characteristics such as race and geographic region as unimportant. Additionally, differences in prior hospitalization, prior hemostat exposure, liver cirrhosis, and obesity were deemed unimportant.”

3rd paragraph: Please clarify the purpose, and definition of the “prior hemostat exposure” co-variate under Methods.

We have defined this variable in the 5th paragraph of the methods as follows:

“Prior hemostat exposure was defined as receipt of a hemostat in any of the hemostat classes including ORC, collagen, gelatin, fibrin sealant, thrombin, flowables, combination products, and adhesion prevention.”

Interpretation of the result can be commented on here and/or elsewhere. Were there many Medicare patients under 65 years old (due to disability and/or ESRD)? If not, differences in the distribution of Medicare patients would be driven by the older age distribution of patients with bleeding complications and is not really an independent covariate.

6th paragraph: If “costs” were based on observed re-imbursement for individual patients, then the distribution of Medicare patients could have affected cost results independent of the effect of the presence or absence of bleeding complications/interventions.

We only included the age variable in multivariate models to avoid violating the assumption of independence between covariates (Medicare status and age). Costs
were not based on observed re-imbursement. Please note the clarification as to how costs are included in the database (Methods section, 4th paragraph).

If post-op transfers TO other acute care hospitals were not included, then listed estimates would underestimate costs of the total inpatient episode of care. Please comment.

We have added a paragraph in the discussion (6th paragraph) to address this issue.

“Second, patients were excluded from analyses if they were transferred from another hospital or an unknown source to ensure that complete hospitalization data were available for every patient. We did not feel that we could reliably identify and link multiple hospitalizations for patients transferred to another hospital using the administration codes in the database. As these transferred patients probably had higher costs relative to the current sample of patients, the exclusion of these patients likely had the effect of underestimating the total inpatient episode of care. Furthermore, if more patients with a bleeding-related complication were transferred to other hospitals versus those without bleeding-related complications, the incremental difference in costs between these groups may in fact be larger than what is currently reported.”

Discussion
The discussion should reflect consideration of issues such as those raised above as they pertain to Methods and Results.

We have added information to the discussion as outlined above to address/discuss many of the issues raised above.

Competing Interests

As this study was entirely industry-funded, the companies involved (United BioSource, Ethicon and Excenda) should be briefly described, and the existence of any products potentially relevant to the study should be briefly noted. For example, it would be useful for readers to if any of these companies makes products that prevent or reduce bleeding complications, since they could benefit directly or indirectly from results showing larger costs attributable to such complications.

We have added the following paragraph to the Competing Interests section to better describe the companies involved in this study:

“United BioSource Corporation is a global scientific and medical affairs organization that partners with life science companies to help generate real-world evidence of product effectiveness, safety, and value to assist health care decisions and enhance patient care. Ethicon is part of the Surgical Care Group of Johnson & Johnson. Ethicon creates products for surgery including topical skin adhesives designed to help heal patients quickly and comfortably without using stitches. Ethicon has also developed women’s health products for the treatment of incontinence, pelvic organ prolapse, and uterine fibroids. Xcenda is a full-service consultancy and managed markets agency that helps manufacturers identify, demonstrate, and deliver their brand’s value proposition to healthcare stakeholders.”