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ORIGINAL RESEARCH

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ABSTRACT

Background: A recent randomized controlled trial showed that patients undergoing ascending aorta surgery treated with HEMOPATCH to control bleeding had a significantly better hemostasis success rate than with dry or wet gauze compression or similar standard of care (SOC).

Objective: To compare the cost-effectiveness using two different agents for hemostasis (HEMOPATCH vs dry or wet gauze compression or similar SOC) in cardiac surgery from the European hospital perspective.

Methods: A literature-based cost-effectiveness model estimating average cost per successful hemostasis event was developed based on the hemostasis efficacy difference (HEMOPATCH = 97.6%, SOC = 65.8%, $p < .001$). Additional clinically significant end-points studied in the trial (blood transfusions and surgical revisions) were also analyzed. It was assumed that each surgery utilized two units of HEMOPATCH (dimensions of 4.5×9 cm) and two units of SOC. Product acquisition costs for HEMOPATCH and SOC were included along with outcome-related costs derived from the literature and inflation-adjusted to 2017 EUR and GBP. Results are presented for an average hospital with an annual case load of 574 cardiac surgeries. One-way and probabilistic sensitivity analyses were performed.

Results: Considering only product acquisition cost, HEMOPATCH had an incremental cost-effectiveness ratio (ICER) of €1,659, €1,519, €1,623, and £1,725 per hemostasis success when compared to SOC for Italy, Spain, France, and the UK, respectively. However, when considering the cost and potential difference in the frequency of transfusions and revisions compared to SOC, the use of HEMOPATCH was associated with an annual reduction of six revisions and 60 transfusions, improving the ICER to €1,440, €1,222, €1,461, and £1,592, respectively. Sensitivity analysis demonstrated model robustness.

Conclusions: This analysis supports the use of HEMOPATCH over SOC in cardiac surgery in European hospitals to improve hemostasis success rates and potential cost offsets from reduced transfusions, complications, and surgical revisions.

Introduction

Peri-operative blood loss during surgical procedures is to be expected; however, blood loss can be especially daunting during cardiac surgery[1,2]. Uncontrolled bleeding during cardiovascular (CV) surgery can necessitate reoperation (2–8% of patients)[3] and/or blood transfusion (45.8% of patients)[4], both of which, independently and collectively, can increase morbidity, mortality, length of stay (LOS) in intensive care unit (ICU) and hospital, and costs[3,4].

Specifically, a Swedish cost analysis showed that re-exploration for bleeding was associated with a significantly greater economic burden, with a cost differential of €6290: 20% of which was due to transfusion use[5]. In Germany, post-CV surgery patients who experienced bleeding incurred significantly higher cost compared to those who didn't (€15,404 vs €8,027; $p < .0001$); resulting in a significant incremental cost of post-operative bleeding of €6,251[6].

Moreover, blood is becoming a progressively scarce resource, due to an increase in complex surgical procedures being performed on older patients. At the same time, the safety and risk of blood supply is becoming a growing concern in Europe. For example, blood donations were halted in two Italian provinces due to an outbreak of Chikungunya (a viral disease transmitted to humans from infected mosquitos) in September 2017[7], leading to a temporary suspension of all planned surgical activities in Rome, Italy. In this context, reducing our dependency on allogeneic blood transfusion to perform safe and effective surgery is becoming increasingly important.

While surgical technique, comorbidities, surgical history, anti-coagulation therapies, type of surgery, and other individual risks may all influence hemostasis during cardiac surgery, surgical technique is the usual culprit for both bleeding and reoperation, signifying the need for effective hemostasis

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strategies[8,9]. Therefore, blood conservation strategies that target rapid and effective intra-operative and post-operative hemostasis (curtailing the need for reoperation and blood transfusion) may be imperative for improved clinical outcomes and cost containment[9–11].

Topical hemostats have been shown to be effective as an adjunct therapy in various surgical applications and especially advantageous in cardiac procedures where traditional hemostatic methods are limited by diffuse microvascular bleeding[11,12]. With the plethora of topical hemostats and limited evidence-based guidelines, hemostatic product selection can pose a challenge. Factors worth considering include mechanism of action, impact on patients' physiology, patients' coagulation abnormalities, malleability, versatility, ease of use and preparation, availability, and cost[11,13]. Beyond these factors, impact on cost and health resource utilization outcomes should be considered as well.

Collagen hemostatic patches have been used for surgical hemostasis and healing for decades and been enhanced since their development in the early 1980s[14,15]. HEMOPATCH is a recently developed hemostatic patch consisting of a specifically formulated collagen matrix, a protein-reactive monomer, and a biocompatible dye[15]. The soft, thin, pliable, high liquid-absorption capacity, self-adherence, and sealing properties of HEMOPATCH make it easy to use in open and minimally invasive surgery[15]. The active side of HEMOPATCH is coated with the rapid protein-reactive monomer, N-hydroxylsuccinimide functionalized pentaerythritol polyethylene glycol ether tetra-succinimidyl glutarate (NHS-PEG). HEMOPATCH has a two-fold mechanism of action. The thin layer of NHS-PEG provides rapid tissue attachment and sealing of the bleeding surface. Additionally, the collagen activates both the coagulation cascade and platelets, and releases coagulation factors, thereby enabling fibrin formation. The clot is further strengthened by the structural collagen fibers[15].

Evidence to support the use of HEMOPATCH was previously limited to several pre-clinical model investigations and case reports[15,16]. In 2014, Fingerhut et al.[18] reported four case series involving the use of HEMOPATCH to control post-operative bleeding related to CV surgery, specifically coronary artery bypass graft (CABG) (2), ascending aorta replacement (1), and CABG reoperation (1). The case series demonstrated the ease of use, flexibility, and rapidity with which HEMOPATCH can be applied to almost any type of CV bleeding surface.

The above findings corroborate the results of a recent prospective randomized clinical trial (RCT) by Weltert et al.[19], which investigated the peri-operative and post-operative efficacy of HEMOPATCH in CV surgery patients undergoing ascending aorta surgery. The results of the RCT showed that, in the HEMOPATCH group vs the SOC group, a statistically higher rate of successful hemostasis was observed, post-operative blood loss was reduced and fewer patients required blood surgical revision and transfusion.

We conducted a follow-up analysis from a European hospital perspective to explore and compare the costs and effectiveness of HEMOPATCH with that of dry or wet gauze compression or similar SOC in CV surgery. Using the clinical differences identified by Weltert et al.[19], we estimate the potential economic savings from the favorable surgical outcomes.

Methods

Overview

A cost-effectiveness model was developed in Microsoft Excel (Redmond, WA) to estimate the annualized clinical and economic impact of HEMOPATCH vs SOC, defined as wet or dry gauze compression, per successful hemostasis event. The model was based on the average number of cardiac surgeries performed in Italian hospitals, accounting for the difference in clinical outcomes between the two products, and the corresponding costs. The model uses the clinical data as published by Weltert et al.[19] and supplemented by additional literature sources. All inputs and their sources are described below.

Clinical inputs

Three clinical inputs from Weltert et al.[19] shown to be either statistically significant (hemostasis success rate) or clinically meaningful (autologous blood transfusion rate within 4 days of surgery and surgical revision rate due to intraoperative bleeding) were included in the model (Table 1). The base case model was run with only the hemostasis success rate, while clinically meaningful variables were included in a secondary analysis.

Cost inputs

European cost inputs were broken down into product costs and surgery-related costs. All costs are country-specific and referenced in Table 2.

Product costs

The cost of product was obtained by multiplying the average product unit amount (i.e. HEMOPATCH $4.5 \times 9\,cm$ size package varieties divided by package size, 3) with publicly available prices (Baxter Average Sales Price (ASP) for HEMOPATCH). The costs of the comparator—wet or dry gauze—was calculated for a variety of brands in all relevant countries and assumed to be the smallest allowable amount

Table 1. Clinical inputs.

Clinical outcomes	HEMOPATCH	SOC	p-value	Data source
Hemostasis success rate	97.6%	65.8%	<.001[a]	Weltert et al.[19], Table II
Need for autologous blood transfusions within 4 days of surgery	23.5%	34.0%	.24	
Need for surgical revision from intra-operative bleeding	4.7%	5.8%	.30	

[a]Significant difference between the groups ($p < .05$).

Table 2. Cost inputs—surgery-related costs.

Surgery-related input categories	Italy (€)	Spain (€)	France (€)	UK (£)	Sources
Product cost for average surgical case					HEMOPATCH ASP per unit in 4.5 × 9 cm pack,
Using HEMOPATCH	263.81	241.53	258.00	274.24	SOC lowest allowable assumption
Using SOC	0.01	0.01	0.01	0.01	
Cost of cardiac surgery, no complication	8,998	8,281	4,553	7,738	Italy[20–22]
Incremental cost of revision	2,086.49	5,581.55	1,943.00	1,521.00	Spain[23–26]
Incremental hospital cost of a single unit allogenic blood product with plasma	222.20	157.09	143.00	121.85	France[21,27,28] UK[29,30]

in the model, at 0.01 EUR or GBP per unit. This provides estimated total product cost figures at the population level, which is relevant from the hospital perspective.

Surgery and complication costs

Literature and practicing Italian surgeon expert opinion validation was used to estimate surgery and complication costs. Surgery-related costs (Table 2) included (1) Average base cost of a cardiac surgery procedure without complications, revision, or blood product transfusion[20–30], (2) Average cost of cardiac surgery procedure with revision, but without complications or blood product transfusion, and (3) Incremental cost of a single unit of allogeneic blood product with plasma. It was conservatively assumed that, on average, one unit of blood was transfused per patient and allogenic blood transfusion cost was utilized based on cardiac surgeon opinion. Autologous blood transfusion in cardiac surgery is no longer relevant in Italy and Europe in general. Costs, where appropriate, have been updated to 2017 EUR or GBP.

Model analyses

The model captures the cost implications between HEMOPATCH and its trial comparator, wet or dry gauze compression, by first evaluating acquisition costs when divided by clinical effectiveness (clinical effectiveness here is defined as hemostasis success rate).

$$\text{Efficiency} = \text{Successful hemostasis events} = 574 \\ \times \text{Hemostasis success rate}$$

$$\text{PC} = \text{Product cost} = 574 \times \text{average product use per surgery} \\ \times \text{unit cost}$$

$$\text{Cost per efficiency} = \text{Product cost}/\text{Successful hemostatis events}$$

In a secondary evaluation, the cost of surgical revision and blood transfusion is added to the product cost, and is divided by the clinical effectiveness end-points.

$$\text{IC} = \text{Incremental cost} \\ = \text{PC} + (574 \times \text{revision rate} \times \text{incremental revision cost}) \\ + (574 \times \text{transfusion rate} \times \text{incremental transfusion cost})$$

The outputs of the cost-effectiveness model were calculated in terms of the comparative clinical outcomes avoided (surgical revisions, transfusions), the associated Incremental Cost Effectiveness Ratios (ICER), defined as the difference between the cost divided by the difference in successful hemostasis events with HEMOPATCH relative to SOC, and the corresponding cost offsets due to reduced revisions and transfusions using HEMOPATCH relative to SOC.

$$\text{ICER}_{PC} = (\text{PC}_{HEMOPATCH} - \text{PC}_{SOC})/ \\ (\text{Efficiency}_{HEMOPATCH} - \text{Efficiency}_{SOC})$$

$$\text{ICER}_{IC} = (\text{IC}_{HEMOPATCH} - \text{IC}_{SOC})/ \\ (\text{Efficiency}_{HEMOPATCH} - \text{Efficiency}_{SOC})$$

Cost offsets were estimated for an average hospital with an annual case load of 574 mixed cardiac surgery patients[31]. These 574 cases were derived from a study of 3,444 patients who underwent cardiac surgery within one of six regional cardiac centers in Italy[31].

Sensitivity analyses

One-way and probabilistic sensitivity analyses were performed on the model's base case estimates to identify the major cost drivers accounting for uncertainty around the estimates.

One-way sensitivity analyses were conducted by varying all clinical and economic inputs one at a time by ±20% for each base input.

Probabilistic sensitivity analysis (PSA) was conducted using a Monte Carlo simulation. All key clinical and economic inputs were varied at the same time by randomly selecting a value for each parameter within ±20% according to a distribution probability. All parameters and the distribution probabilities can be found in Appendix Tables 1A and 2A.

Results

Base model

The primary outcome of the model shows an ICER of €1,659, €1,519, €1,623, and £1,725 when considering only hemostasis success rate, respectively, in Italy, Spain, France, and the UK. As a secondary evaluation, the model was updated using clinically significant end-points (surgical revisions and transfusions), and the ICER was reduced to €1,440, €1,222, €1,461, and £1,592, respectively. A lower ICER indicates that HEMOPATCH is even more cost-effective than SOC when considering the clinically significant end-points.

For European hospitals performing an average of 574 mixed cardiac surgeries annually, using HEMOPATCH over SOC (wet or dry gauze compression) would avoid six surgical revisions and 60 transfusions with allogenic blood product with plasma. The avoidance of surgical revisions and transfusions resulted in substantial annual cost offsets of €39,958 in
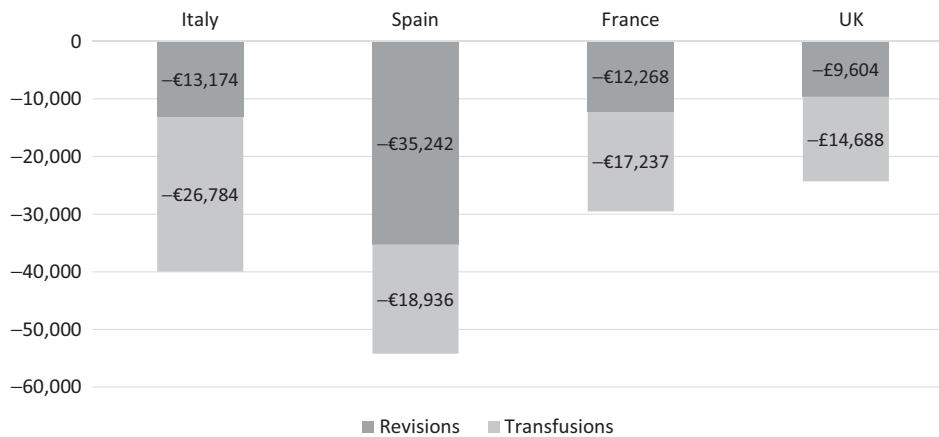
Figure 1. Estimated cost impact of reduced revisions and transfusions using HEMOPATCH vs SOC in an average Italian hospital performing 574 cardiac surgical procedures per year.

Italy, €54,178 in Spain, €29,505 in France, and £24,291 in the UK. Figure 1 shows these annual cost offsets, per hospital per annum, for avoided surgical revisions and transfusions in each country of interest.

Sensitivity Analyses

Varying each model parameter one at a time in the one-way sensitivity analyses showed that HEMOPATCH's cost offsets due to reduced revisions and transfusions within the same 574 patient cohort ranged from €22,612–€57,304 in Italy, €17,013–€91,342 in Spain, €16,568–€42,443 in France, and £14,164–£34,419 in the UK.

The most important cost drivers were: (1) the ratio of autologous blood transfusions within 4 days of surgery, (2) the ratio of surgical revisions due to intra-operative bleeding, and (3) the average amount of product used per surgery (Figure 2(a–d)). Variation in the cost of hemostatic agents and the hemostasis success rate did not have an impact on the cost offsets due to reduced revisions and transfusions. In all analyses, the difference was always in favor of HEMOPATCH consistently demonstrating cost offsets.

When varying all parameters at the same time in the PSA, the two-tailed 95% confidence interval of cost offsets due to reduced revisions and transfusions associated with HEMOPATCH ranged from €13,171–€73,497 in Italy, €4,511–€111,255 in Spain, €6,769–€56,172 in France, and £7,209–£44,789 in the UK (Figure 3(a–d)). Approximately 46% of Italian, 48% of Spanish, 51% of French, and 49% of British simulations were above the base case and, thus, the model's cost offsets of €39,958 in Italy, €54,178 in Spain, €29,505 in France, and £24,291 in the UK can be considered a relatively robust estimate in approximating the benefit of using HEMOPATCH relative to SOC.

Discussion

We found that each additional case of successful hemostasis achieved with HEMOPATCH would only cost a hospital €1,659 in Italy, €1,519 in Spain, €1,623 in France, and £1,725 in the UK when considering only hemostasis success rate.

While acquisition costs for HEMOPATCH are considerably higher than the SOC, Weltert et al.[19] clearly demonstrated that HEMOPATCH provided significantly better hemostatic efficacy. This model helped us assess the cost-effectiveness of using HEMPATCH in cardiac surgeries to stop bleeding.

The avoidance of surgical revisions and transfusions resulted in substantial cost offsets in all countries explored and, therefore, reduced the cost of achieving hemostasis to €1,440 in Italy, €1,222 in Spain, €1,461 in France, and £1,592 in the UK. We estimated that the average Italian hospital that utilizes HEMOPATCH in cardiac surgery procedures may see a reduction of six surgical revisions and 60 transfusions with allogenic blood product with plasma.

After adjusting all clinical and cost inputs, HEMOPATCH's cost offsets for the same 574 patient cohort ranged from €22,612 to €57,304 in Italy, €17,013 and €91,342 in Spain, €16,568 to €42,443 in France, and £14,164 and £34,419 in the UK. Furthermore, in the PSA, after 1000 iterations, HEMOPATCH's cost offsets two-tailed 95% confidence interval ranged between €13,171–€73,497 in Italy, €4,511–€111,255 in Spain, €6,769–€56,172 in France, and £7,209–£44,789 in the UK. Thus, both types of sensitivity analyses indicated the robustness of the cost offsets associated with use of HEMOPATCH vs SOC.

Our results presented here are more conservative than those published by Corral et al.. Corral et al.[17] estimated cost savings for EVARREST vs SOC gauze and were able to include OR time, which drove the largest proportion of cost savings. Unfortunately, Weltert et al.[19] did not report OR time and, since no sources were identified to understand how much extra surgeon time was required when hemostasis was unsuccessful during CV surgeries, we have not modeled this potential benefit.

In the specific context of hemostasis, the efficacy of a technique or a technology grants a better outcome for the patient, but also other tangible and non-tangible resource utilization advantages to the hospital-health system: faster procedures, less time spent in operating theatres, less energy and resources spent monitoring blood loss, on-site tests for coagulation, administering pro-coagulation drugs, etc. Each of these steps has a direct cost, measurable in money, and an indirect cost, which includes amongst others consumption
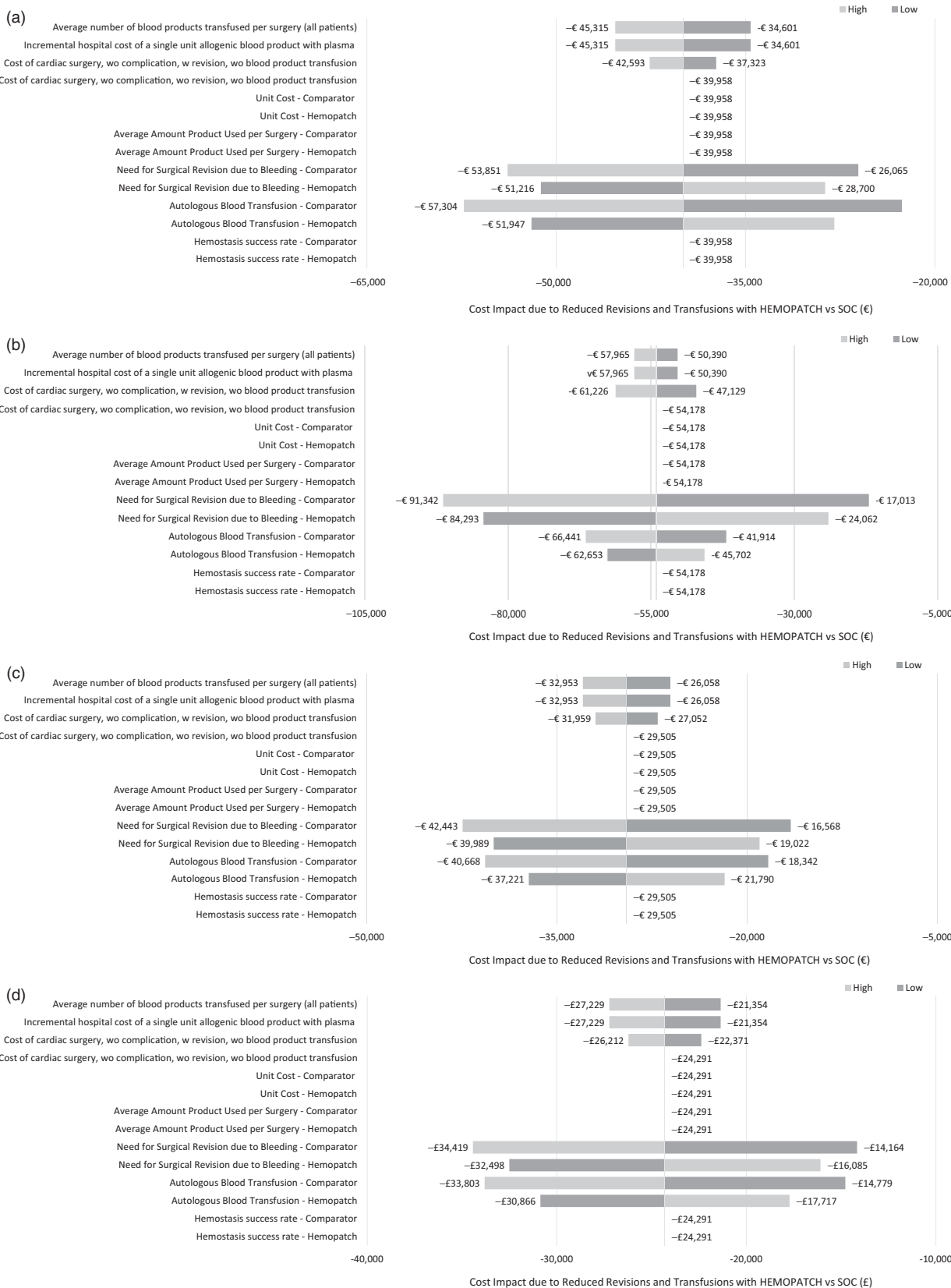
Figure 2. One-way sensitivity analysis results for (a) an Italian, (b) a Spanish, (c) a French, and (d) a British Hospital Performing 574 Cardiac Surgeries per Year.

of caregivers' time and attention. Hence, in an era of constrained resources and budgets, it is important to compare the economics of various hemostatic agent/strategies to control bleeding.

Lastly, although the end-points of surgical revision and transfusion derived from the Weltert et al.[19] analysis were only numerically lower and not statistically significant in the HEMOPATCH vs the SOC group, we deemed it clinically
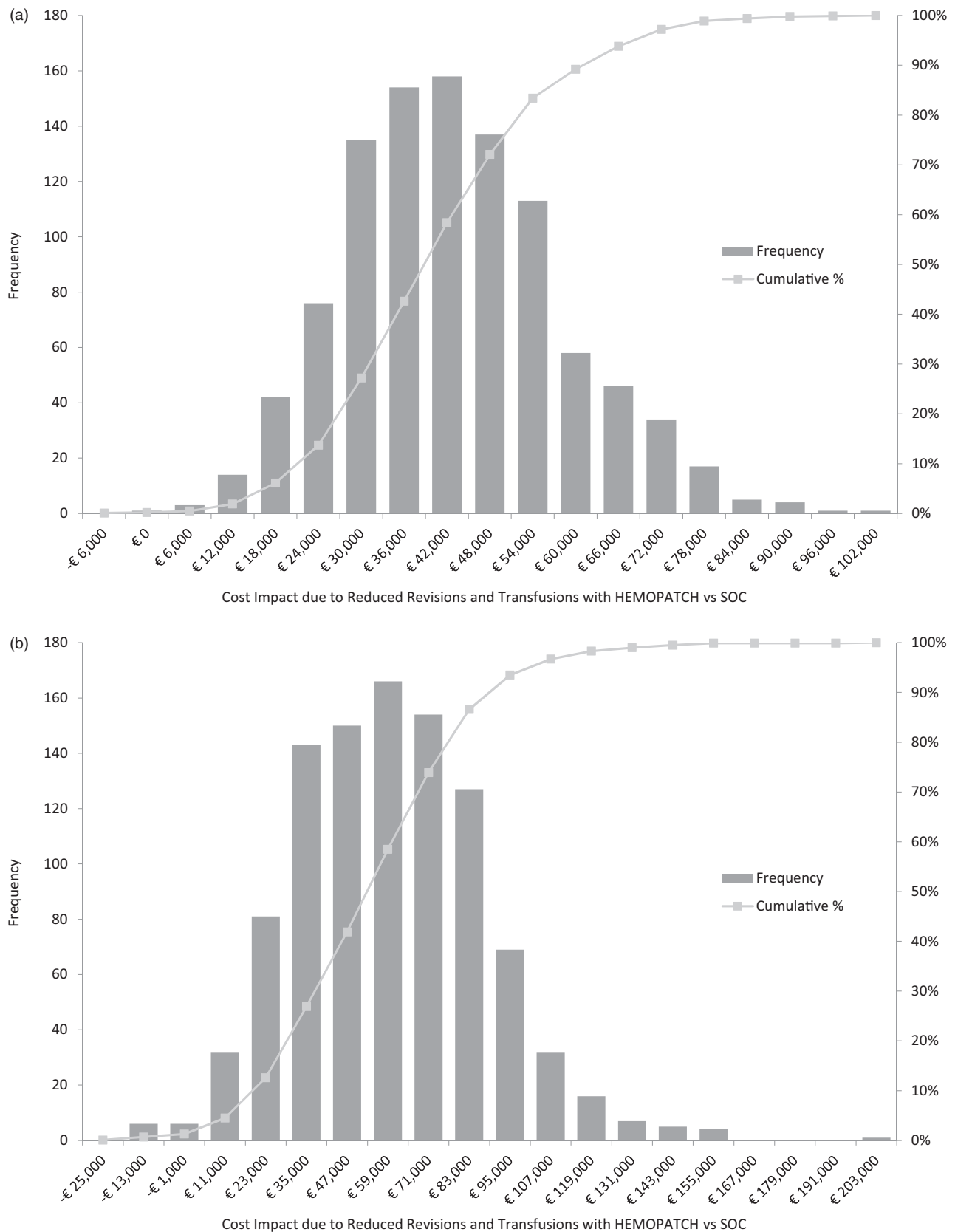
Figure 3. PSA results for (a) an Italian, (b) a Spanish, (c) a French, and (d) a British Hospital Performing 574 Cardiac Surgeries per Year.

relevant to include it in our economic analysis, due to the high clinical and economic burden of surgical revision and transfusion in CV surgery. For example, Stone *et al.*[32] reported a 1-year mortality rate of 6.4%, which was positively correlated with transfusion of any blood products as well as greater units of red blood cells (RBC) administered. In the same way, total per-patient healthcare costs are significantly greater in those who experience bleeding, as well as in those
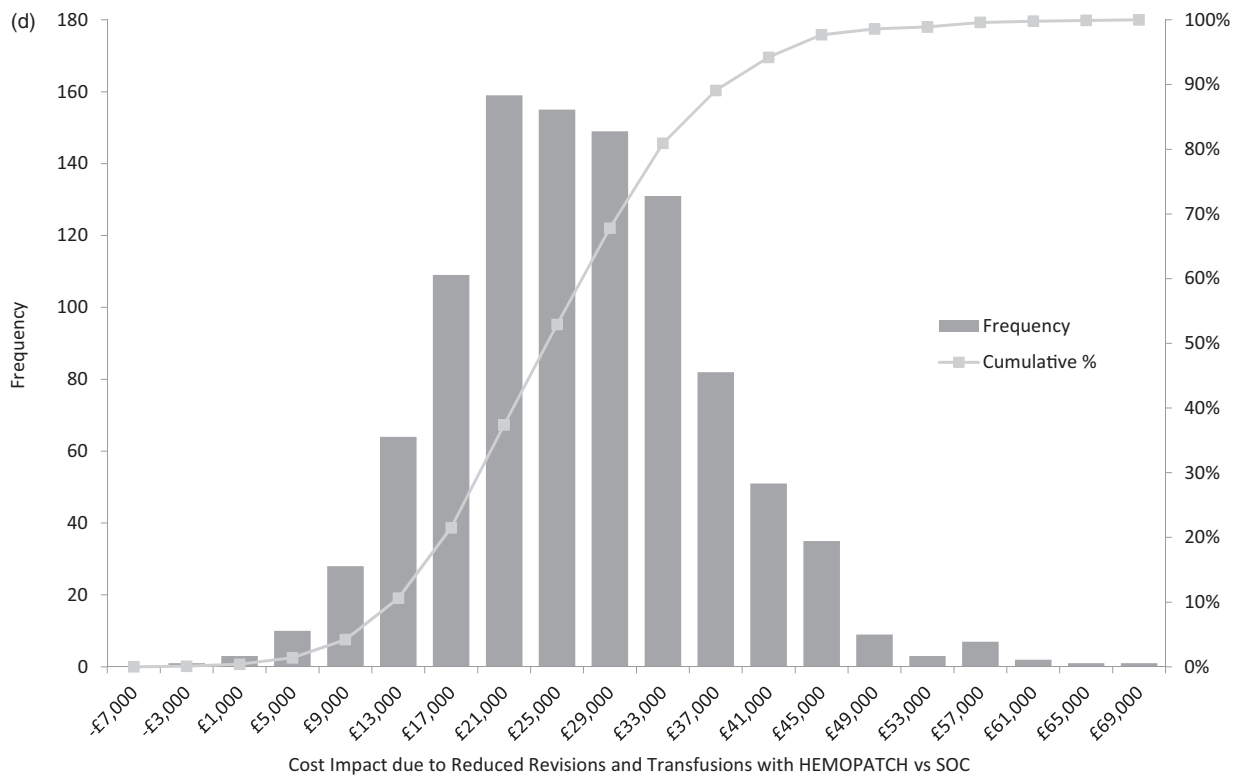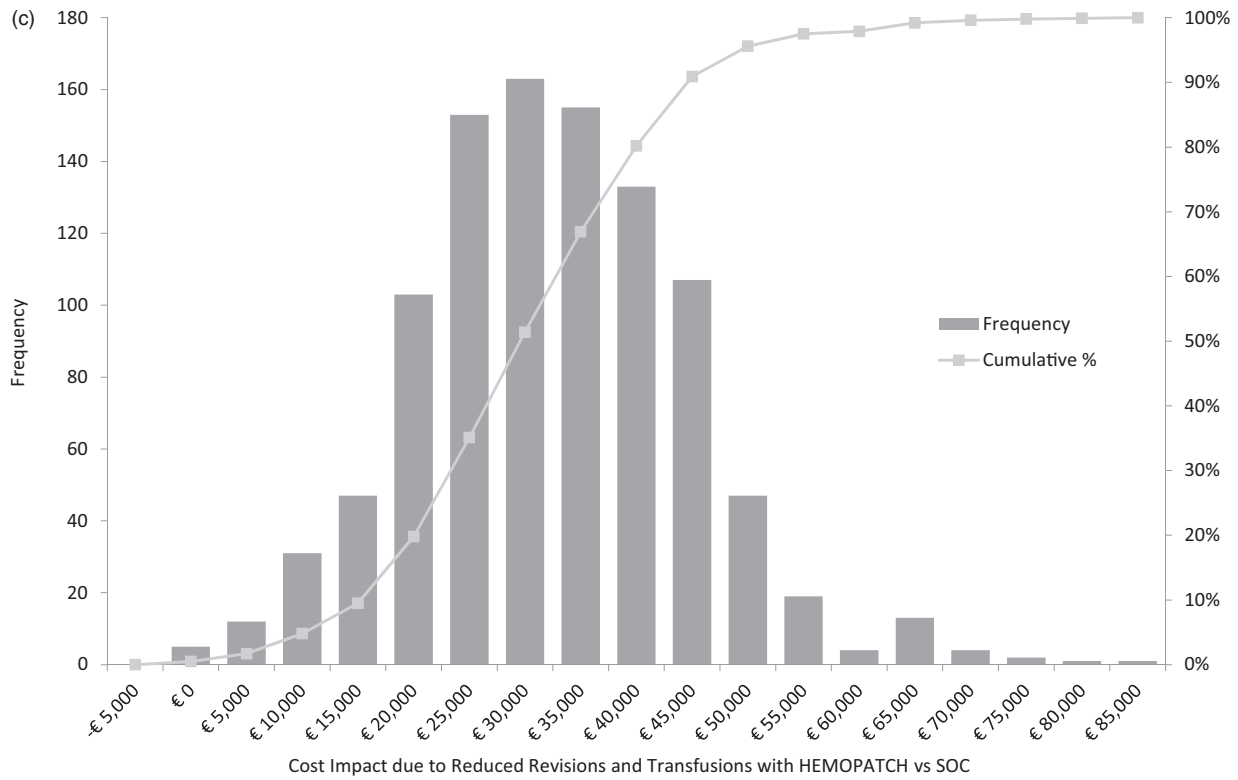
(c)

Cost Impact due to Reduced Revisions and Transfusions with HEMOPATCH vs SOC

(d)

Cost Impact due to Reduced Revisions and Transfusions with HEMOPATCH vs SOC

Figure 3. Continued.

who undergo re-operation/exploration for bleeding[5]. In the era of value based purchasing and high clinical and economic burden of uncontrolled bleeding in CV surgery, the cost avoidance derived from transfusion and surgical revision reduction in our analysis are notable and worth considering in hemostatic product selection.

Limitations

All economic models are a simplification of a complex healthcare situation and, hence, bear the limitations associated with a simple representation of the reality. For example, our model assumed the same distributions for average number

of blood products transfused per cardiac surgery, irrespective of hemostat choice. This may not be the case in reality, but we had no solid evidence supporting a different assumption.

While model results are highly dependent on the nature, amount and quality of the data available, we included clinical results identified in the RCT study published by Weltert et al.[19], and our results remained robust after performing one-way and probabilistic sensitivity analysis. Observational cost data would further strengthen the analysis, but were not available to the authors.

Our model was built for the European healthcare environment (i.e. using clinical evidence and costs from European sources), and, although it is very relevant for Italian, French, Spanish, and British hospitals, the generalizability of our results should be adjusted to other jurisdictions.

Finally, the cost offsets due to reduced revisions and transfusion with HEMOPATCH vs SOC were presented for an average case load of 574 hospitals, as reported in a regional cardiac center in Italy[31]. It is likely that not all CV or ascending aorta surgery cases will require HEMOPATCH and, therefore, this may be an over-estimate. Given the number of CV surgeries will vary substantially by hospital, it is encouraged that results are adjusted for the relevant number of cases. It is noted that the ICER results are independent of sample size.

Conclusion

This cost-effectiveness analysis supports the use of HEMOPATCH over standard of care in cardiac surgery, as it offers a statistically significant higher hemostasis success rate which may lead to sizable cost offsets from reduced transfusions, complications, and surgical revisions. By choosing HEMOPATCH over SOC, annualized cost offsets of €39,958 in Italy, €54,178 in Spain, €29,505 in France, and £24,291 in the UK are expected to be realized in hospitals performing an average of 574 cardiac surgical procedures per year. Various sensitivity analyses demonstrated the robustness of this estimate. Further research should be focused on determining the consistency of these results in other surgery types.

Transparency

Declaration of funding

Declaration of financial/other relationships

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Appendix

Table 1A. Probability distributions for clinical inputs

Parameter	Base estimate	Probability distribution
Average number of cardiac surgical procedures per year	574	Log normal
Hemostasis success rate - HEMOPATCH	0.98	Log normal
Hemostasis success rate - SOC	0.66	Log normal
Surgical revisions		
Ratio for surgical revision due to intra-operative bleeding - HEMOPATCH	0.05	Log normal
Ratio for surgical revision due to intra-operative bleeding - SOC	0.06	Log normal
Blood product transfusions		
Ratio for autologous blood transfusion - HEMOPATCH	0.24	Log normal
Ratio for autologous blood transfusion - SOC	0.34	Log normal

Table 2A. Probability distributions for cost inputs.

Parameter	Base estimate	Probability distribution
Italy		
HEMOPATCH unit cost	263.81	Log normal
SOC unit cost	0.01	Log normal
Cost of cardiac surgery, without complication, without revision, without blood product transfusion	8,998.63	Normal
Incremental cost of revision	2,086.49	Gamma
Incremental hospital cost of a single unit of allogenic blood product with plasma	222.20	Log normal for incremental cost
Average number of blood products transfused per surgery	2	Log normal
Spain		
HEMOPATCH unit cost	241.53	Log normal
SOC unit cost	0.01	Log normal
Cost of cardiac surgery, without complication, without revision, without blood product transfusion	8,281.22	Normal
Incremental cost of revision	5,581.55	Gamma
Incremental hospital cost of a single unit of allogenic blood product with plasma	157.09	Log normal for incremental cost
Average number of blood products transfused per surgery	2	Log normal
France		
HEMOPATCH unit cost	258	Log normal
SOC unit cost	0.01	Log normal
Cost of cardiac surgery, without complication, without revision, without blood product transfusion	4,553	Normal
Incremental cost of revision	1,943	Gamma
Incremental hospital cost of a single unit of allogenic blood product with plasma	143	Log normal for incremental cost
Average number of blood products transfused per surgery	2	Log normal
UK		
HEMOPATCH unit cost	274.24	Log normal
SOC unit cost	0.01	Log normal
Cost of cardiac surgery, without complication, without revision, without blood product transfusion	7,738	Normal
Incremental cost of revision	1,521	Gamma
Incremental hospital cost of a single unit of allogenic blood product with plasma	121.85	Log normal for incremental cost
Average number of blood products transfused per surgery	2	Log normal