Willingness to pay for eliminating the risk of being infected by blood-borne diseases in regular replacement treatment for patients with haemophilia

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Abstract: Hemophilia is a set of lifelong bleeding disorders linked to the X chromosome. Standard treatment for patients with severe hemophilia is intensive replacement therapy with intravenous injection of coagulation factor concentrates to prevent spontaneous recurrent joint bleed. In the 1980s, many hemophilia patients were infected with HIV and/or hepatitis C transmitted by plasma derived coagulation factor concentrates. In the future, new pathogens could appear and a risk remains that the current manufacturing methods will not be able to eliminate those. The aim of the study is to estimate the value of eliminating the risk of being infected by blood-borne diseases in the treatment of hemophilia which could provide decision-makers with information on how much resource to spend on this purpose to be in line with societal preferences. Individual preferences for safety were elicited from a sample of 821 individuals from the Swedish general population using a web-based questionnaire. The preferences were estimated using the “chained approach” which combines the contingent valuation (CV) and standard gamble (SG) methods. The respondents were asked (1) to state their willingness-to-pay to avoid a temporary, non-fatal injury presented in a health state derived from the EQ-5D instrument, and (2) to choose between living with this injury with certainty or receive a treatment that could restore the respondent to full health immediately, but which entails a risk of being infected by a fatal, blood-borne disease. A value of a statistical life (VSL) in the context of blood-borne diseases of SEK47 million was calculated by “chaining” the answers to the CV question and SG question, and from the VSL we derived a value of a QALY in the context of blood-borne diseases of SEK2.8 million. Using the current mean annual dose of factor concentrate of 268,000 international units (IU) per patient in Sweden, the value of eliminating the risk of being infected by blood-borne diseases would be SEK1.80 per IU corresponding to a price premium of around 45 %.

JEL classification: D6

Key words: willingness to pay, hemophilia, recombinant factor VIII concentrates, regular replacement treatment, chained approach, preferences

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1 Introduction

Medical treatment of disease may entail risks and rigorous safety reporting for medicines are standard since decades. For diseases where medicines are manufactured from human blood, the risk of virus transmission is a central concern. People with hemophilia have an X chromosome-linked bleeding disorder associated with a lack of blood coagulation factors. Hemophilia is included among the rare diseases (Mannucci and Tuddenham, 2001) with a prevalence of 1 in 10,000 in the general population. (Berntorp and Shapiro, 2012) The replacement treatment with intravenous infusions of the deficient clotting factor introduced in hemophilia care in the 1960s has drastically increased the life expectancy which now approaches that of the general population. (Darby et al., 2007, Lovdahl et al., 2013) Besides the risk of life threatening bleeds, repeated bleeding episodes in joints lead to crippling hemophilic arthropathy. Patients therefore use clotting factor concentrates both to treat and prevent bleeds.

Clotting factor concentrates manufactured from blood plasma or using plasma proteins in the process could be susceptible for viral transmission. In the 1980s, many people with hemophilia were infected with human immunodeficiency virus (HIV), acquired immunodeficiency syndrome (AIDS) and/or hepatitis C (HCV), all of which were acquired through infected plasma-derived factor concentrates. (Darby et al., 2007, Evatt, 2006, Soucie et al., 1998) HIV infection occurred in up to 70% of people with severe factor VIII deficiency in many countries and in 30% to 40% of the hemophilia population as a whole. The majority of people with hemophilia were also infected with hepatitis B and/or hepatitis C. Prior to the HIV and HCV outbreaks, life expectancy amongst the hemophilia community in developed countries had been increased from 16 years at the start of the 20th century, to 60 years in 1980. (Arnold et al., 2006, Darby et al., 2007, The Swedish Haemophilia Society, 2003, O'mahony, 1999) However, by 1994 it had fallen to 40 years, almost entirely as a result of AIDS. (Chorba et al., 1994)

Today, the manufacturing of coagulation factor concentrates includes various methods to eliminate the transmission of known pathogens, and these methods are effective. However, while some pathogen risks are now well-understood, other existing pathogens remain an unknown threat. For emerging pathogens we do not know if the current methods will have the ability to eliminate the pathogens. There are reports of parvovirus contaminants in coagulation factor concentrates (Sharp et al., 2012) and non-enveloped viruses can be difficult to completely remove via current methods of virus inactivation. (Modrow et al., 2011, Emea, 2001)

Recombinant factor concentrates are produced via cell line based technologies and use human- or animal-derived materials at various stages of processing, that is they may still involve a risk for viral transmission. (Masac, 2006) However, in 2003, a new plasma and albumin-free method for manufacturing recombinant factor concentrate was introduced in the treatment of factor VIII-deficient patients (the product ADVATE®, Baxter BioScience). Removal of all animal- or human-derived raw materials or additives from biopharmaceutical manufacturing eliminates the threat of infectivity by known and other, yet unknown prions. (Grillberger et al., 2009)

Safety per se has a value to individuals which is revealed on the private market where consumers are prepared to pay for safety (e.g. food safety, safety equipment). For products where no private market exists, as is the case with factor concentrates in the treatment of hemophilia in Sweden, the contingent valuation method (CVM) can be applied to elicit the value people place on viral safety of medicines. The CVM is a method where individuals are asked to state what they would be willing to pay (WTP) for non-market goods or services on a hypothetical market.

The CVM has been shown to be theoretically valid (Bateman and Langford, 1997) and to have convergent validity (Clarke, 2002). However, one of the most important weaknesses of the CVM is scale bias which appears when an increase of the good being valued does not lead to a corresponding increase of the WTP as stated by the respondent. The more unfamiliar the good and the smaller the risk, the more anomalies seems to arise. (Bateman et al., 2002) As a response to this challenge, Carthy et al (Carthy et al., 1999) have developed an alternative approach – the so called “chained approach” - that breaks down the valuation process of the standard CV approach in two more manageable steps.

Although patients with hemophilia may be more familiar to the commodity being valued, it would not be possible to reach a sufficiently large sample for this rare disease. It will therefore be necessary to elicit preferences among the general population, which is often considered appropriate since they are the real payers of the commodity through taxes.

Eliciting the value of eliminating the extremely small risk of being infected by a currently unknown blood-borne disease for the general population using the CVM may be at risk at causing scale bias. The purpose of this study is to apply the “chained approach” for the estimation of the value of eliminating the risk of being infected by blood-borne diseases in the treatment of hemophilia.

2 Methods

2.1 The Chained Approach

This study applied the chained approach (Carthy et al., 1999) to elicit the value of a statistical life (VSL) in the context of blood-borne diseases among a sample of the Swedish general population. The VSL is the sum of money which a large group of people is willing to pay to reduce the risk of one fatality within this group. For example, assume that there is an intervention which will reduce the risk of death from 5 per 100,000 and year to 4 per 100,000 and year in a group of 100,000 people. This means that 1 statistical life will be saved each year. Applying the CVM, means asking for the WTP for this intervention directly (e.g. what is the maximum amount you would be willing to pay to reduce your risk of death from 5 in 100,000 to 4 in 100,000 per year?). Assuming that the mean individual WTP for the intervention is €50 per year means that the entire group is willing to pay €5,000,000 ($€50 * 100,000$) to save one statistical life, which is equal to the mean marginal rate of substitution (MRS) of wealth for risk of death for individuals in the affected group.

Applying the chained approach means eliciting the MRS of wealth for risk of death using a two-step procedure which aims to facilitate the valuation task for the respondent.

The *first* part of the chained approach is aimed at finding the WTP to avoid the certainty of a minor and familiar health loss (e.g. injury) and the willingness to accept (WTA) to sustain the same injury with certainty. These estimates are used to infer the implicit MRS of wealth for risk of the minor health loss. Later applications of the chained approach do, however, rely exclusively on the WTP estimate (Alberini et al., 2010, Donaldson, 2010), and this study follows that procedure. The *second* part of the chain is aimed at finding the risk of the major health loss (what the survey aims to value, e.g. as in our case a blood-borne disease) which is equivalent to the certainty of the minor health loss through the use of a slightly modified version of the standard gamble (SG) approach. By chaining the estimates from the first and second part it is possible to infer the implicit MRS of wealth for risk of death from blood-borne disease, i.e. the VSL. This method has been shown to be sensitive to scope, easy to understand, internally consistent, and has been used by Carthy et al (1999) with results that were accepted by the Department of Transportation

in the UK. (Bateman et al., 2002, Carthy et al., 1999, Donaldson et al., 2011, O'reilly et al., 1994)

In this study we use the chained approach to elicit the value of eliminating the risk of a fatal blood-borne disease. The rationale for excluding non-fatal blood-borne diseases from the analysis is that it would make the survey too complicated and lengthy, and thereby increase the risk of unreliable answers. The first part of the chain, i.e. the WTP question, was framed as an opportunity to buy a complementary insurance to cover the cost of a treatment that would restore the respondent to full health (described as a health state derived from the EQ-5D-3L, and labeled “the pink health state”) immediately *if* the respondent would suffer a temporary road traffic injury (described as a health state derived from the EQ-5D-3L and labeled “the orange health state”) within the next 12 months (risk was said to be 1 in 1000). This differs from the approach employed by Carthy et al which aims at finding the WTP to avoid a minor health loss with certainty. The reason for framing the WTP question as an opportunity to buy insurance is to include demand side uncertainty and limit the income effect. The second part of the chain, i.e. the SG question, was framed as a choice between two treatments (X and Y) in a situation where the respondent would die without treatment. Treatment X would leave the respondent with reduced quality of life for a year (the same health state as was avoided when paying for the complementary insurance in the WTP-part). Treatment Y would restore the respondent to full health immediately but included a risk of a blood-borne disease which would lead to death within a year. The risk of a blood-borne disease was varied until the respondents’ indifference between treatments could be interpreted. A small risk of death (1 in 1000) was included in treatment X to make the respondent gamble.

By chaining the answers to the WTP-question and SG-question it will be possible to calculate the VSL in the context of blood-borne diseases (equation 1).

$$(1) \quad VSL_B = (WTP/(1/1,000))/(SG - 1/1,000)$$

The WTP for the insurance is first divided by 1/1,000 to gain the WTP to avoid the temporary road traffic injury with certainty. The resulting WTP is then divided by the risk of a blood-borne disease in the SG question minus 1/1,000 (i.e. the incremental risk). To obtain an estimate of the value (V1) of eliminating the risk of death from blood-borne disease associated with plasma-derived FVIII in the treatment of hemophilia, the risk of death from blood-borne disease associated with plasma-derived factor concentrate (1 %)¹ was multiplied by the VSL in the context of blood-borne diseases (VSL_B), see equation (2).

$$(2) \quad V1 = 0.01 \times VSL_B$$

To check the validity of the result from using the chained approach we applied a second approach to elicit the value (V2) of eliminating the risk of a fatal blood-borne disease. This approach meant asking the respondent to rate the utility of a hemophilia health state (U_H, described as a health state derived from the EQ-5D-3L as measured on the relevant population (Miners et al., 1999), labeled “the brown health state”) with (U_{HR}) and without (U_{HNR}) a risk (R) of death (corresponding to the risk of death associated with plasma-

¹ The risk that a certain year will contain exposure to the infectious disease is 0.15 (treatment with plasma-derived factor concentrates has been given since 1970, i.e. for approximately 40 years, and during six of these years, 1980-1985 the patients were exposed to the risk of being infected by a fatal blood-borne disease, i.e. HIV). The risk of being infected during a year of exposure is 0.07 (17 of 300 patients receiving factor concentrates were infected by HIV during each year of exposure). Thus, the risk of being infected with a currently unknown, fatal virus is approximately 0.01 (0.15 x 0.07) per year.

derived FVIII in the treatment of hemophilia, i.e. 1% per year) using the SG approach. From this we can elicit the loss in quality of life from exposure to a risk of death in the hemophilia health state. This can then be transformed into a money metric by multiplying this loss with the value of a quality-adjusted life-year (QALY, i.e. one year in full health) in the context of blood-borne disease (VQALY_B) derived from the VSL estimated using the chained approach (equation 3 and 4).

In order to calculate the value of a QALY based on the VSL (VQALY_B), we used a method which has been used and validated by previous studies (equation 3) (Mason et al., 2009). The VSL is divided by the expected remaining QALYs of the population discounted at 3 % which is calculated from survival statistics (Sch, 2010), quality-of-life data (Kind et al., 1999), and the age distribution of the respondents.

$$(3) \quad VQALY_B = VSL_B / \text{number of QALYs}$$

$$(4) \quad V2 = (U_{HNR} - U_{HR}) \times VQALY_B$$

2.2 Questionnaire

A web-based questionnaire was constructed which contained three parts (Figure 1). The first part included background questions (age, sex, income etc.). In the second part, the respondent was introduced to the survey and to the concept of risk and willingness to pay. The third part included four different situations to elicit the preferences of the respondents.

Figure 1: Flow chart of the questionnaire (dashed boxes are scenarios used in the chained approach)

Situation 1 and 2 were designed to elicit the VSL in the context of blood-borne disease by using the chained approach.

Situation 3 and 4 were designed to elicit the utility of a hemophilia patient receiving treatment with and without risk of death, respectively, using the SG approach.

The situations included descriptions of three health states derived from the EQ-5D-3L (Table 1). The details of the scenarios are described in the Appendix.

Table 1: Health state descriptions used in the questionnaire

Health State	Health State Description (based on EQ-5D-3L)
Pink Health State ^a (Full Health)	No problems in walking about No problems washing or dressing myself No problems doing usual activities (for example work, studies, household activities, leisure) No pain or discomfort Not anxious or depressed
Orange Health State ^a (Severe Injury)	Slight problems in walking about Slight problems washing or dressing myself Severe problems doing usual activities (for example work, studies, household activities, leisure) Moderate pain or discomfort Moderately anxious or depressed
Brown Health State ^a (Severe Hemophilia)	Slight problems in walking about No problems washing or dressing myself Slight problems doing usual activities (for example work, studies, household activities, leisure) Moderate pain or discomfort Not anxious or depressed

^a Each health state was illustrated by adding a smiley. The pink health state was illustrated by using a pink, happy smiley. The orange health state was illustrated by using an orange, sad smiley. The brown health state was illustrated by using a brown, sad smiley.

To ensure that the WTP-question would deliver valid answers we applied methods which have been shown to reduce biases common in CVM (e.g. hypothetical bias, starting point bias), including the card-sorting procedure, control question for non-payers (Bateman et al., 2002), and certainty calibration for payers (Blumenschein et al., 2008).

A “card-sorting procedure” was applied to elicit the WTP of the respondent. Different amounts (payments for one year, SEK10; 50; 100; 350; 500; 1000; 5000; 8000; 10000; 30000) were presented one at a time in a mixed order and the respondent was asked to answer if she would be willing to pay the amount, would not be willing to pay the amount or if she was unsure. After responding to these questions for every amount presented, the respondent was presented with the highest amount that she would pay and the lowest amount she would not pay and was then asked to state the highest amount that she would pay. The

answer to this final open willingness-to-pay question was interpreted as the WTP of the respondent.

An interval division approach similar to the one used in Euro-Vaq (Donaldson, 2010) was applied to elicit the point of indifference in the SG-questions. The respondent was asked to choose between treatment X (Scenario 2: orange health state for one year and 1 in 1000 risk of death; Scenario 3: brown health state for rest of life and no risk of death; Scenario 4: brown health state for rest of life and 1 in 100 risk of death) and treatment Y (Scenario 2: pink health state within one week and between 2 and 99 in 1000 risk of death; Scenario 3 and 4: pink health state within one week and between 1 and 99 in 100 risk of death). A maximum of four questions were asked, varying the risk of death associated with treatment Y depending on the answer of the respondent (Figure 2). If the respondent was not indifferent between treatments at any of the four questions asked, the intermediate risk (between the highest risk rejected and accepted, respectively) was assumed to be the point of indifference.

Figure 2: Interval division approach in the SG scenario

Note: Risk of death with treatment Y in the SG question for scenario 2 (the same approach was applied to SG-question for scenario 3 and 4, divided by 100 instead of 1000), grey box = starting point, black box = prefer treatment Y, white box = prefer treatment X, end-nodes = interpreted risk of indifference.

2.3 Subjects and Data Collection

A sample of 1,500 individuals from the adult (18 years or older) Swedish general population was randomly selected from an online panel in the Cint Panel Exchange (CPX) (total adult panel population, $n = 170\,000$). The CPX is an online panel market place where panel owners can join and allow access to their panels to online sample buyers. Panels are recruited by different type of sources, including telephone, face to face, online and email.

Data was collected by using the web-based questionnaire during the period April 2-9th 2012. The web-based questionnaire was piloted before main data collection. The answers were collected automatically and could not be traced back to the respondent. The

respondents were offered incentives for their time corresponding to points which could be transformed into cash, used for online purchases, or make payments to charity or other associations. The incentives have been set to encourage long term participation and to discourage professional respondents who seek to respond to surveys only to obtain payment.

2.4 Data Analysis

Statistical analyses were conducted using SPSS version 12.0 (SAS Institute Inc., Cary, NC, USA). All respondents who completed the questionnaire (i.e. who did not chose to exit before completion) were included. Willingness to pay is reported in SEK (SEK1 = €0.11, exchange rate 2015-07-28 (Valuta.se, 2015)).

A common problem when eliciting WTP is how to handle respondents who refuse to answer, state a zero WTP, or an implausibly high WTP. (Bateman et al., 2002) The WTP of the respondents who chose to skip the open WTP question was interpreted as the highest amount they answered that they were willing to pay in the card-sorting procedure. If the answer could not be interpreted (e.g. if the respondent was unsure about all pre-defined amounts in the card-sorting procedure and did not respond to the open WTP-question), the respondent was excluded from the base-case analysis.

Zero responses were considered protest bids if their exclusive answer to the control question for those not wanting to pay anything was that the government should pay. The true valuation of these respondents was assumed not to be zero but unknown, and they were therefore excluded from the base-case analysis.

Implausibly high WTP was defined according to the outlier definition of a box plot, i.e. a value that is more than 1.5 times the interquartile range larger than the 75:th percentile. Excluding these observations implies a conservative estimation of the WTP.

The relationship between income (transformed to a continuous variable by using the middle for each income group) and WTP was assessed using a multiple regression analysis, with answers to the log of the open WTP question as the dependent variable and age, sex, number of adults, number of children, education, the log of income per consumption unit (Scb., 2009)), risk estimation, risk anxiety, and answer to certainty question as explanatory variables.

The difference between the utilities estimated in situation 3 and 4 was analyzed using a Wilcoxon Signed Ranks Test.

A p-value <0.05 was considered significant.

3 Results

3.1 Subjects

The questionnaire was mailed to a sample of 1,500 persons from the Swedish adult general population in an online panel. 1,003 (67 %) started to answer the questionnaire and 821 (55 %) completed the questionnaire. Among those who did not complete the questionnaire, 6 were excluded because they were under the age of 18, 13 were excluded because of technical problems, and 163 chose to exit the questionnaire before completion. More than half (89) of these chose to exit the questionnaire when they were asked to answer if they would be willing to pay something for the insurance (Situation 1), 44 chose to exit before situation 2, and 38 chose to exit before situation 3.

Of those who completed the questionnaire, 45 % were women, the average age was 48 years, approximately two thirds lived in households with at least 2 adults, 77 % lived in households with no children, 55 % had a university education, 45 % were employed, and the mean household income were SEK 39,802 per month (Table 2, column 2). Compared

to the entire Swedish adult population, the respondents had similar mean age (Scb, 2015c), income (Scb, 2015b) and share of households with children (Scb, 2015a) but had a slightly lower share of women (Scb, 2015c), employed (Scb, 2012) and single households (Scb, 2015a) and were more educated (Scb, 2015d) (column 3, Table 2).

Table 2: Descriptive statistics for the respondents who completed the questionnaire (n=821)

Characteristic	Proportion or average (SD)	Adult Swedish population ^b
Proportion of women	44.8	50.4
Mean age	48.3 (18.5)	49.0
Mean household income, SEK/month	39,802 (20,069) ^a	38,076
Number of adults in the household		
1	28.1	39.5
2 or more	71.9	60.5
Number of children in the household		
0	76.5	73.3
1 or more	23.5	26.7
Level of education		
Elementary school	8.4	16
2y secondary school	11.6	23
3-4y secondary school	28.0	23
University	52.0	37
No information	3.0	2
Occupation		
Employed	45.2	53
Self-employed	4.3	6
Retired	30.1	26
Student	10.7	3
Unemployed	5.5	5
Parental leave	0.5	-
Sick leave	3.8	3
Respondent's perception of their own risk of a severe injury from a road traffic accident compared to population average		
Lower	49.7	
Equal	37.0	
Higher	4.1	
Don't know	9.1	
Risk anxiety ^b		
Not at all anxious	53.8	
A little anxious	39.3	
Somewhat anxious	5.6	
Anxious	0.6	
Very anxious	0.6	

^a Income was given as intervals in survey. The mid-value of each income interval was used to construct a continuous variable. ^b Based on information collected from Statistics Sweden (SCB). (Scb, 2012, Scb, 2015c, Scb, 2015b, Scb, 2015a, Scb, 2015d)

3.2 The value of a statistical life (VSL) and the value of a QALY (VQALY) in the context of blood-borne diseases based on the chained approach

More than 90 % (n = 749 of 821) of the respondents would pay at least SEK 10 per year for the insurance. Consistent with theory, fewer respondents were prepared to pay the higher predefined amount to pay (Figure 3).

Figure 3: Proportion of respondents agreeing to pay for the insurance at different bids in the card-sorting procedure

109 (23 %) respondents were excluded from the base-case analysis of the open WTP question, whereof 37 because their WTP could not be interpreted, 7 because their reason for not being willing to pay was that the government should pay (i.e. protesters), and 65 because they were defined as outliers (Figure 4). The base-case sample thus included 712 respondents.

The mean WTP of the base-case sample was SEK 2,122 (SD: SEK 2,152) per year, whereof those who were definitely sure had a slightly lower WTP (N=218; SD SEK 1,985) compared to those who were probably sure (N=479; SEK 2,239). The mean WTP for the full sample of respondents completing the questionnaire including outliers and applying a zero WTP to not interpretable respondents and protesters was SEK 3,370 (SD: SEK 7,386).

The result of a regression with log WTP as the dependent variable is presented in Table 3. The WTP was, consistent with theory, significantly related to the income of the respondents ($p < 0.0001$). Being probably sure was close to significantly positively related to WTP ($p = 0.056$) which correspond to expectations.

Figure 4: Frequency distribution of the answers to the open WTP question, striped bars represent respondents who were excluded from the base-case analysis **Table 3: Regression of log willingness-to-pay (WTP) for the base case sample^a**

Parameter	Coeff.	95 % CI		p-value
Constant	1.648	-0.598	3.894	0.150
Female	0.155	-0.048	0.357	0.134
Age (y)	-0.002	-0.007	0.004	0.595
Log income per CU ^b	0.518	0.288	0.747	<0.0001*
Education	0.035	-0.070	0.139	0.517
More than one adult	0.060	-0.157	0.278	0.586
Child in household	0.060	-0.189	0.310	0.635
Risk estimation	-0.035	-0.153	0.084	0.565
Risk anxiety	0.029	-0.117	0.174	0.696
Probably certain on WTP	0.206	-0.005	0.418	0.056

^a Excluding respondents who did not want to answer to income or education question or who did not receive the certainty question, ^b CU=Consumption Unit; *Statistically significant. $R^2=0.048$, $n=568$, $F=3.088$.

123 (15 %) respondents did not gamble, i.e. they still preferred living with the road traffic injury when the risk of dying from the curative treatment was 2 in 1,000 (the lowest risk in the standard gamble). Another 85 respondents were indifferent or preferred the curative treatment when the risk of dying was 2 in 1,000. These were categorized as “not definitely” gambling.

The mean risk of a fatal blood-borne disease in the curative treatment where the respondents were indifferent between the treatments was 32 per 1,000 (median: 15/1,000) among all respondents (N=821), 38 per 1,000 (median: 34/1,000) among “gambling” respondents (N=698), and 43 per 1,000 (median: 40/1,000) among “definitely gambling” respondents (N=613).

Based on the mean response of the “definitely certain” respondents in the WTP question and of the “definitely gambling” respondents in the SG question, the VSL is MSEK47 and the value of a QALY would then correspond to MSEK 2.8 in the context of blood-borne diseases (Table 4).

Table 4: The value of a statistical life (VSL) and the value of a QALY in the context of blood-borne diseases based on the answers to situation 1 and 2 (the chained approach)

	N	Mean (SD)	Median
Situation 1 (SEK/year)	218 ^a	1985 (2058)	1000
Situation 2 (Risk of death Y)	613 ^b	0.043 (0.034)	0.040
VSL ^c	-	47.3 MSEK	25.6 MSEK
Value of a QALY (VSL/QALYs ^d)	-	2.8 MSEK	1.5 MSEK

^a Respondents who answered definitely sure to the certainty question and who were not defined as an outlier or protester; ^b Respondents who accepted a risk of death of 5/1000 or more in treatment Y; ^c VSL=(WTP/(1/1,000))/(SG-1/1,000); ^d Based on the age distribution of the respondents: 16.64.

3.3 Utility of a hemophilia patient receiving treatment with and without risk of death from bloodborne disease

137 (17 %) respondents did not gamble in situation 3 (where the “certain” option included no risk of death). 84 (10 %) respondents did not accept the curative treatment or were indifferent between the treatments at a risk of 1 per 100 in situation 4 (where the “certain” option included a risk of death). These respondents behaved irrationally since both treatments were associated with a risk of death of 1 per 100, but the curative treatment would result in better health. Furthermore, 442 respondents rated the utility of the brown health state *with* risk higher compared to the same brown health state *without* risk. The answers of these respondents were also considered irrational.

The mean utility of severe hemophilia with and without risk was 0.79 (median: 0.91) and 0.77 (median: 0.89) respectively among all respondents, i.e. contrary to what would be expected. When excluding all non-gambling and non-rational respondents, the mean utility of the brown health state with and without risk was 0.66 (median: 0.79) and 0.83 (median: 0.92) respectively. The difference was statistically significant ($p < 0.0001$). (Table 5)

Table 5: Utility of the brown health state (severe hemophilia) without risk of death from blood-borne disease (situation 3) and with risk of death from blood-borne disease (situation 4)

	N	Mean (SD)	Median
Situation 3 (1-risk of death Y)	213 ^a	0.83 (0.21)	0.92
Situation 4 (1-risk of death Y)	213 ^a	0.66 (0.30)	0.79

^a Respondents who gambled and accepted a higher risk of death in treatment Y when treatment X involved risk.

3.4 Value of risk elimination of blood-borne disease in the treatment of hemophilia

We used the results from the study to calculate the value of the risk elimination of blood-borne disease in treatment of hemophilia (Table 6). There are two approaches to doing this. In the first and main approach, the estimated risk reduction (1 %) is multiplied using the VSL_B from Table 3 (equation 2 above). In the second and supportive approach, the gain in utility from the risk reduction estimated using the difference in mean utility from situation 3 and 4 (0.17; Table 5) is multiplied with the $VQALY_B$ from Table 4 (equation 4 above). Despite differences in approaches, the resulting value of risk elimination was similar and nearly SEK 500,000 per person per year.

The value of risk elimination in hemophilia care can be further illustrated by relating the value per person per year to the expected average annual use of factor concentrate for people aged 30 years or older with deficiency of factor VIII (268,000 international units, IU, (Tlv, 2011)). This means that the estimated gain of recombinant factor VIII produced with a plasma and albumin free method compared to plasma-derived coagulation factors would amount to SEK 1.80 per IU.

Table 6: Value of eliminating the risk of death from blood-borne disease based on two approaches

Approach	Gain per Year	Value per Unit (million SEK)	Value of the Gain per Year (SEK)	Value per IU ^a (SEK)
Main (equation 2)	0.01 VSL	47.3	472,619	1.76
Supportive (equation 4)	0.17 QALYs	2.8	482,844	1.80

^a With a dose of 268,000 IU per year per patient.

4 Discussion

This study estimated the value of eliminating the risk of being infected by a currently unknown, fatal blood-borne disease in the treatment of hemophilia patients to SEK1.8 per IU. In a value-based pricing system adopting a societal perspective – such as the one applied by the Dental and Pharmaceutical Benefits Agency (TLV) in Sweden – prices of pharmaceuticals are set according to their societal value. The result of this study would thus support a price increment of 45 % (SEK1.8/SEK4 per IU (Fass, 2015)) for recombinant factor VIII produced with a plasma and albumin free method relative to plasma-derived coagulation factors. The value is applicable to the risk elimination when replacing plasma-derived factors, which have a known, historical risk of blood-borne diseases, with the third generation recombinant factor VIII concentrates, which entails no risk of blood-borne diseases. The risk of a currently unknown, fatal blood-borne disease from plasma-derived pharmaceuticals was estimated to one percent per year based on historical data on the HIV outbreak in the 1980s and 1990s. Since then, various effective methods to eliminate the transmission of *known* pathogens have been implemented. However, it is unclear if these methods will have the ability to eliminate currently *unknown*, emerging pathogens. Therefore, this study is based on the assumption that the historical risk of plasma-derived pharmaceuticals is the best available estimate of the current risk.

The demographic characteristics of respondents appeared to be representative of the adult Swedish population. The primary method for checking the validity of a WTP survey is to analyze if the WTP is related to the income of the respondents. This was shown to be the case in this study ($p < 0.0001$). Furthermore, the respondents' answers were generally consistent with theory, e.g. fewer respondents were prepared to pay the higher predefined

amount to pay (i.e. in accordance with a demand curve). This study followed the practice of WTP-studies and excluded protesters and outliers from the base case analysis. The majority of those were outliers and their inclusion would have led to a higher WTP.

The method applied in this study deviates from the original version of the chained approach in three ways. It relies exclusively on WTP to derive the MRS of wealth for risk of the minor injury instead of using both WTP and WTA, it applies an insurance-based approach in the WTP scenario, and the chaining is based on mean response instead of individual response. The implication of these deviations put together is unclear. Excluding WTA would lead to an underestimate, but using an insurance-based approach would lead to an overestimate compared to WTP to avoid an injury with certainty. Chaining on mean response will lead to a lower estimate, but tends to limit the effect of extremes. (Baker et al., 2010)

The primary analysis kept a conservative approach and was based on the definitely certain WTP respondents and the definitely gambling SG respondents (Table 3). Previous studies have shown that the WTP of the definitely certain respondents tends to be lower and correspond more to the real WTP compared to the WTP of the probably sure respondents (Blumenschein et al., 2008). However, limiting the analysis to a restricted sample may reduce the representativeness of the result.

The application of the WTP approach in health care have raised some concern since interventions with relatively small benefits are valued disproportionately high – due to scope and scale effects – and since the interventions being evaluated are valued higher on its own than when evaluated together with a range of other interventions – due to ‘budget constraint bias’. (Cookson, 2003) This study applies the chained approach to limit the problem of scale effects. The ‘budget constraint bias’ may still exist, but may have been reduced by using a conservative approach in the analysis.

A weakness of this study was that a large number of respondents answered questions 3 and 4 irrationally, i.e. provided a higher utility rating for hemophilia with risk compared to the utility for hemophilia without risk. The reason for this is unclear. However, these questions came at the end of the questionnaire and there may have been respondents who were tired of reading and understanding the questions.

There were a number of non-traders in the SG questions (scenario 2: 15 %, scenario 3: 17 %, scenario 4: 10 %). The share of non-traders are not always reported in SG studies, Carthy et al (1999) (Carthy et al., 1999) being one exception. They found that 16 of 167 (10 %) respondents did not gamble in the modified version of the chained approach, i.e. similar to this study. One reason for the non-trading in scenario 2 and in Carthy et al (1999) might be that respondents are asked to accept an increase in the risk of death to avoid a temporary health loss. However, this cannot be the only reason for non-trading since the share is higher or almost as high in scenario 3 and 4, where respondents were asked to accept a risk of death to avoid a permanent health loss.

The mean VSL estimated in this study was SEK47 million, which is about two times as large as the estimate which is used for road traffic accidents in Sweden (SEK23 million, 2011 years prices). There are however reasons why the reduction of the risk of blood-borne diseases is highly valued.

First, this study framed the WTP question as an opportunity to buy insurance, i.e. the scenario described a private good. This is contrary to when the WTP is framed as a public good – e.g. doing investments in roads by raising taxes – which is the approach used to estimate the VSL in road traffic accidents. Research shows a large positive difference between private WTP and public WTP (Svensson and Vredin Johansson, 2010).

Secondly, research has shown that there is a premium for risk reductions when death follows after a period of substantial morbidity and/or generates a fear that is greater than

would be justified by its objective risk probabilities.(Viscusi et al., 2014) For example, people's WTP for a given risk reduction has been found to be more than two times as large when traveling by air compared to by taxi (Carlsson et al., 2004), and there has been shown to exist a cancer premium above the VSL associated with acute accidents.(Viscusi et al., 2014) The type of death involved in this study, i.e. a currently unknown fatal blood-borne disease, can be expected to generate a fear that is greater than what would seem justified since it is neither voluntary nor controllable which are aspects known to increase fear. (Carlsson et al., 2004).

This study shows that individuals value an elimination of the risk of blood-borne diseases by a substantial amount. An earlier study ranked viral safety of products in hemophilia care as the most important among seven attributes for three groups of stakeholders (Mantovani et al., 2005) Along with the result of this study, this further emphasizes the value of viral safety in the treatment of patients with hemophilia.

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Appendix

Scenario description

These are translated versions of the scenario description as they were displayed in the web-based questionnaire.

Situation 1: WTP-question to avoid orange health state

Different amounts (payments for one year, SEK10; 50; 100; 350; 500; 1000; 5000; 8000; 10000; 30000) were presented one at a time in a mixed order. After responding to each amount, the respondent was presented with the highest amount that she would pay and the lowest amount she would not pay and was then asked to state the highest amount that she would pay in an open question.

Now assume that the risk that you will get severely injured in a road traffic accident within one year is 1 in 1000. If you get injured you will live with the orange health state for one year.

The orange health state

Consider what it would mean for you to live with this health state.

Slight problems in walking about	
	Slight problems washing or dressing	
	Severe problems doing usual activities (for example work, studies, household activities, leisure)	
	Moderate pain or discomfort	
	Moderately anxious or depressed	

Now imagine that you could buy an insurance that would cover the cost of a treatment which would make you return to full health more quickly if you get injured. Within one week you would return to full health and live with the pink health state.

The pink health state

Consider what it would mean for you to live with this health state.

No problems in walking about	
	No problems washing or dressing myself	
	No problems doing usual activities (for example work, studies, household activities, leisure)	
	No pain or discomfort	
	Not anxious or depressed	

Without insurance:

- The risk that you will get injured within one year is 1 in 1000.
- If you get injured you will receive standard treatment X.
- The treatment means that it will take one year before you return to full health. During this year you will live with the orange health state.

With insurance:

- The risk that you will get injured within one year is 1 in 1000.
- If you get injured you will receive standard treatment X and the additional treatment Y.
- The treatment means that you will return to full health within one week.
- Buying this insurance is the only way to get access to treatment Y.

We will now show you a number of amounts in random order. Given your household's current income, would you pay the amount, NOT pay the amount, or are you uncertain/don't know? When you're thinking about what the insurance would be worth, you should assume that your household will have the same income as today if you are ill and cannot work, i.e. you don't need to insure for income loss.

Situation 2: SG-question to avoid orange health state (risk of death due to blood-borne disease)

A maximum of four questions were asked, varying the risk of being infected with a fatal virus in alternative Y (between 2 and 99 in 1000) depending on the answer of the respondent. If the respondent was not indifferent between alternative X and Y in any of the four questions asked, the intermediate risk (between the highest risk rejected and accepted, respectively) was assumed to be the point of indifference.

Now assume that you have suffered a severe injury in a road traffic accident. Without treatment you will end up unconscious which will result in death within a short period of time.

Now imagine that there are two alternative treatments to choose from. The first treatment means that you will live with **the orange health state** for one year before you return to full health.

The orange health state

Consider what it would mean for you to live with this health state.

Slight problems in walking about	
	Slight problems washing or dressing	
	Severe problems doing usual activities (for example work, studies, household activities, leisure)	
	Moderate pain or discomfort	
	Moderately anxious or depressed	

The second treatment means that you will return to full health (**the pink health state**) within a week. But there is a risk that you will be infected with a fatal virus when you receive this treatment since this treatment includes a pharmaceutical which is derived from blood from donators.

The pink health state

Consider what it would mean for you to live with this health state.

No problems in walking about	
	No problems washing or dressing myself	
	No problems doing usual activities (for example work, studies, household activities, leisure)	
	No pain or discomfort	
	Not anxious or depressed	

Alternative X. Bad health for one year	Alternative Y. Uncertain curative treatment
<ul style="list-style-type: none"> You will live one year with the orange health state before you return to full health. The risk that you die during this year is 1 in 1000. 	<ul style="list-style-type: none"> You return to full health (the pink health state) within one week. The risk of being infected with a fatal virus (which leads to death within one year) is 40 in 1000.

In this situation, would you prefer treatment X, treatment Y, or do you consider both of them to be equally good?

Situation 3 and 4: SG-question to avoid hemophilia without (situation 3) and with (situation 4) a risk of death

A maximum of four questions were asked, varying the risk of death in alternative Y (between 1 and 99 in 100) depending on the answer of the respondent. If the respondent was not indifferent between alternative X and Y in any of the four questions asked, the intermediate risk (between the highest risk rejected and accepted, respectively) was assumed to be the point of indifference.

Now assume that you have a severe form of bleeding disorder (hemophilia). Without treatment you will die within one year. Now imagine that there are two alternative treatments to choose from. The first treatment (treatment X) means that you will live with **the brown health state** for the remaining part of your life.

The brown health state

Consider what it would mean for you to live with this health state.

Slight problems in walking about	
	No problems washing or dressing myself	
	Slight problems doing usual activities (for example work, studies, household activities, leisure)	
	Moderate pain or discomfort	
	Not anxious or depressed	

The second treatment (treatment Y) means that you will return to full health (**the pink health state**) within a few days. But there is a risk of failure, which means that you will end up unconscious which will lead to death within a short period of time.

The pink health state

Consider what it would mean for you to live with this health state.

No problems in walking about	
	No problems washing or dressing myself	
	No problems doing usual activities (for example work, studies, household activities, leisure)	
	No pain or discomfort	
	Not anxious or depressed	

Alternative X. Chronic disease	Alternative Y. Uncertain curative treatment
<ul style="list-style-type: none"> You will live the rest of your life with the brown health state. [Only situation 4]: The risk that you die from the treatment is 1 in 100. [Only situation 4]: Your risk of death is the same as that of a healthy person after the first year 	<ul style="list-style-type: none"> You return to full health (the pink health state) within one week. The risk that you die from the treatment is 40 in 100.

In this situation, would you prefer treatment X, treatment Y, or do you consider both of them to be equally good?