UNIVERSITA' DEGLI STUDI DI NAPOLI FEDERICO II
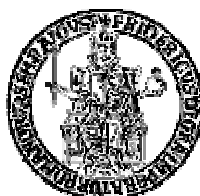
FACOLTA' DI FARMACIA

DOTTORATO DI RICERCA

IN

SCIENZA DEL FARMACO

XXI CICLO

Health Technology Assessment for Rare Diseases:

Evaluation of Preferences toward treatments for

Patients with Haemophilia

Candidato: Dott.ssa *Luciana Scalone*

Tutor: Chiar.mo Prof. *Lorenzo Giovanni Mantovani*

Coordinatore: Chiar.ma Prof.ssa *Maria Valeria D'Auria*

Anno accademico 2007-2008

INDEX   **PAG**

ABBREVIATIONS

aPCC = activated prothrombin complex concentrates

DCA = Discrete Choice Analysis

DCE = Discrete Choice Experiment

FVIII = factor VIII

ITI = immune tolerance induction

HRQoL = health related quality of life

MRS = marginal rates of substitution

NHS = National Health Service

PCC = prothrombin complex concentrates

QoL = Quality of Life

RUT = Random Utility Theory

rFVIIa = recombinant activated factor VII

RI =Relative importance

WTP = willingness to pay

SUMMARY

Rationale

Despite the success of recent investments in health technology for the treatment in hemophilic patients, today, inhibitor development is a major complication of hemophilia treatment, as inhibitors increase the risk of uncontrollable bleeding, make surgery more problematic, increase the risk of severe physical disabilities, reduce wellbeing, and represent a potential cause of premature mortality.

The introduction of new options, such as immune tolerance induction and the use of bypassing agents, has significantly improved treatment success in inhibitor patients in even the most challenging situations (e.g. emergencies, home treatment, and surgery). However, these treatment advances are paralleled by significant increases in the cost of care for these patients, and economic constraints can cause limited access to optimal therapy. In order to optimize the benefits derived from use of the available resources, it is necessary to know and compare both present and future effects and costs of alternative options. Identification of the most efficient option allows implementation of appropriate investments, which must be considered as opportunities to improve patients' health and wellbeing. Implementing rational investments may also facilitate economic benefits in the future, with potential advantages not only for patients, but also for their families and for society as a whole.

However, there is still a lack of consensus on how to optimally treat haemophilia patients with inhibitors. Considerable uncertainty remains about the optimum treatment choice in different clinical circumstances. Furthermore, in several healthcare systems, resource constraints are main potential obstacles for access to the most efficient treatment options. As a result, clinicians have for several years made decisions on how to manage their patients according to their own experience and opinions. These decisions can differ

depending on the type of patient, on the bleeding situation, and on possible considerations related to safety, immunogenicity, practicalities, product availability, and costs.

The management of these patients actually involves a complex interaction between different parties, i.e. physicians, patients or their caregivers, and budget holders. Each of these parties has their own set of preferences, which is influenced by the role they play in the healthcare system, their experiences, and their expectations. In order to optimise the appropriateness of the decisions, it is necessary to be both informed and aware of the opinions and preferences of the interested parties. This knowledge can be useful in order to better understand the potential benefits of treatments, thereby improving the success, and possibly also increasing the efficiency, of the intervention.

Objective

This work aimed to evaluate preferences towards the characteristics of different coagulation factor concentrates for haemophilia inhibitors patients, from the perspective of patients or their caregivers, haematologists, pharmacists.

Methods

A discrete choice study was conducted. Potential products were described with eight selected characteristics: perceived viral safety, risk of anamnestic response, possibility of undergoing major surgery, frequency of infusions in prophylaxis, number of infusions to stop bleeding, time to stop bleeding, time to pain recovery, cost. Participants received 16 pairs of potential products and chose from each pair the option they considered better. Data were analyzed with a random-effects conditional logistic model.

Results

1614 observations were obtained from 37 patients/caregivers, 39 physicians, and 25 pharmacists from Italy. Cost, in terms of additional healthcare taxes, was the most important attribute to every group: the relative importance assigned to this characteristic was 21% by the patients/caregivers and 26-27% by the physicians and pharmacists, suggesting that unlike to what it may be thought, cost is an important issue also to people not directly involved in the payment for these products.

For patients/caregivers the next most important factors were: risk of anamnestic response (RI = 20%), possibility of undergoing major surgery (RI = 18%), perceived viral safety (RI = 18%). For physicians the next most important characteristics were: risk of anamnestic response (RI = 18%), number of infusions to stop bleeding (RI = 14%), possibility of undergoing major surgery (RI = 13%). For pharmacists the next most important factors were: time to stop bleeding (RI almost 20%), time to pain recovery (R = 14%), possibility of undergoing major surgery (RI = 13%).

Discussion

To our best knowledge this is the first study estimating and comparing the value given by patients (or their caregivers), physicians, and pharmacists to the different characteristics of coagulation factor concentrates used for the treatment of haemophilia patients with inhibitors. Not only outcome attributes, such as those related to safety, like viral and risk of anamnestic response, those related to effectiveness, like the time to stop a bleeding, the time to alleviate the pain and possibility of undergoing major surgery, but also process attributes (frequency of infusions to stop a bleeding or to follow a prophylaxis regimen) and cost are considered important for a product used in patients with inhibitors.

Decisions on treatments must take into account patients' characteristics and their clinical needs; however, preferences can also play an important role in the choice and success

of treatments. The results of this study could, therefore, help decision-makers to optimise the overall benefits of treatments.

INTRODUCTION

The disease

Hemophilia is a rare disease due to inherited coagulation defects that cause spontaneous and post-traumatic bleeding. The prevalence of this disease in Italy has been established recording data provided by 35 hemophilia centers in a computerized national registry: hemophilia A affects 0.82/10,000 males in the general population, of which 64% are severely affected. Hemophilia B affects 0.15/10,000 males, of which 70% are severe [1]. In other Western countries, the estimated prevalence of hemophilia is similar to that in Italy [2, 3]. In patients with hemophilia, bleeding and its complications in muscles and joints often lead to disability, extreme pain and impairment of the overall quality of life. In recent years the availability of more effective drugs has generally improved management of patients with hemophilia. Because of the cost of treatment and the complex nature of the disease that warrants a multisciplinary approach, the health care of patients with hemophilia absorbs a large amount of economical and human resources and can be taken as an example of the socio-economic impact of biotechnologies in rare diseases [4-6].

Development of inhibitors against treatment with coagulation factor concentrates

The development of inhibitory antibodies in hemophilic patients treated with clotting factor concentrates is one of the most challenging complications of hemophilia treatment, as it inactivates the coagulation factor activity, hence compromises the efficacy of the mainstay of treatment, i.e., factor replacement [7].

The overall prevalence of inhibitors in patients with hemophilia A or B is estimated to be approximately 9% and 3% respectively; patients with moderately severe (factor levels 1-

5%) and severe hemophilia A (<1%) have a greater risk of developing inhibitors, with a reported prevalence between 7% and 20% [8-13].

This complication makes the treatment of bleeding episodes more difficult, increases the risk of uncontrollable haemorrhages, and makes the performance of surgery more problematic, with important consequences in terms of disability, poor well-being, and premature death [9, 11, 12, 14-17].

Inhibitors predominantly develop in early childhood, during the initial phase of treatment with coagulation factor concentrates. Inhibitor development has been found to be related to a number of possible endogenous and exogenous factors such as genetic, ethnic/racial or family reasons, type and severity of haemophilia, exposure to replacement concentrates, and treatment regimen [8, 18-27].

Treatment of patients with inhibitors

Special therapeutic approaches are used in inhibitor patients to reduce the antibody level [15, 28], such as the induction of immune tolerance [29, 30] and plasma exchange with or without immunoadsorption on protein A columns. Although the implementation of immune tolerance induction (ITI) has facilitated the eradication of inhibitors in a number of patients [16, 31], this approach is not actually efficacious in around 30-40% of cases [9, 32, 33]. In addition, not all patients are considered suitable candidates for ITI: for example, patients with long-standing inhibitors, those with further difficulties with treatment, those at an increased risk of serious bleeding complications, and those with chronic joint diseases. Factor VIII (FVIII) derived from porcine plasma (porcine FVIII) with a lower antibody cross-reactivity, and agents bypassing the coagulation defect, such as prothrombin complex concentrates (PCC), activated prothrombin complex concentrates (aPCC) [10, 34, 35], and recombinant activated factor VII (rFVIIa) [36-38], have been successfully adopted in a

number of these challenging situations, including emergency, home treatment, and surgery [10, 28, 29, 35, 38-47], in which they contribute to prolonging patients' life expectancy and improving health related quality of life (HRQoL) [48, 49].

According to recent data from a naturalistic Italian Cost of Care Inhibitors Study (named COCIS) [48], the current management of adult patients with inhibitors leads to relatively good levels of wellbeing. This study observed 52 patients (aged 15–64 years) for up to 18 months: their orthopedic condition was found to be compromised, with 73% of patients having impaired range of motion in at least one main joint (hip, knee, wrist). Other frequent signs or symptoms related to a compromised orthopedic functioning were crepitus (71.2% of the patients), flexion contractures (69.2%), and axial deformity (57.7%). Regarding HRQoL 63% reported difficulties in walking (as ascertained by the 'mobility' domain of the EQ-5D questionnaire [50]); 34% reported difficulties with taking care of themselves (e.g. washing or dressing); 54% reported difficulties with performing usual activities (e.g. work, study, housework, family or leisure activities); 78% had moderate or severe pain or discomfort; and 38% declared themselves to be moderately or severely anxious or depressed. HRQoL assessed with the SF-36 instrument [51, 52] was shown to be, on average, lower for inhibitor patients than for the general population comparable for age and sex. A relationship between inhibitor patients' orthopedic functioning and the physical component of their HRQoL was also found [53], particularly for issues such as mobility, self-care, daily activities and perception of pain and/or discomfort: problems in these domains were reported more frequently by patients with more compromised orthopedic functioning. In contrast, the mental component of wellbeing is not particularly affected by the presence of inhibitors, as no association was found with orthopedic problems. One interpretation of these findings is that, while chronic and irreversible orthopedic disabilities affect the physical health of inhibitor patients, the awareness that effective interventions are available allows

patients to cope well with their clinical condition and to preserve relatively good levels of mental QoL

More recently, a naturalistic European study on the orthopedic status of patients with hemophilia and inhibitors (ESOS), conducted by Morfini and colleagues in several European countries [54], confirmed the relationship between orthopedic complications and QoL in inhibitor patients. Problems with mobility, self-care, performing usual activities, and pain/discomfort were reported more frequently by inhibitor patients, while there were no significant differences in the prevalence of anxiety and depression between inhibitor and non-inhibitor patients. This study also found that patients with inhibitors typically have significantly more joint abnormalities, and consume more resources, than those without inhibitors.

On the other hand, the management of hemophiliacs with inhibitors is particularly costly, both in absolute terms and in comparison with the treatment of hemophiliacs without inhibitors [55, 56]. Treatment cost is a major issue to be considered in hemophilia care, as significant increases in costs have paralleled advances in healthcare. For instance, the cost of treatment for adult patients with inhibitors corresponds to an average of around €200,000 per patient per year [49]– more than twice the mean cost of treatment for patients with moderate to severe hemophilia without inhibitors [57]. The majority of costs (99%) are attributable to the use of coagulation factor concentrates, while almost 50% is attributable to the use of rFVIIa, which is widely used to manage both spontaneous and surgical (including orthopedic) bleeding episodes. As a consequence, although effective strategies are currently available to meet inhibitor patients' needs (e.g. management of bleeding, performance of orthopedic surgery), the huge amount of resources consumed in recent years actually limits use of the best available options in some healthcare systems [58-65].

Of interest in this regard is what emerged from a discussion between US hemophilia care providers about the issues that influence treatment choices for high-titer inhibitor patients [64]. The cost and supply of bypassing agents were found to be critical determinants in choice of product for almost half the participating physicians. One panelist stated that his hospital dictated that rFVIIa could only be used after other treatment options had been exhausted. Furthermore, many physicians noted that their large public hospitals have established stringent rules for approval of rFVIIa use.

Solimeno and colleagues [61] reported that, although total joint replacement is now the treatment of choice for hemophilia patients with chronic hemophilic arthropathy of the knee and hip in developed and developing countries, the same cannot yet be said for hemophilic patients with inhibitors: elective surgery in these patients today is still limited to a few centers and extremely few subjects. The availability of rFVIIa has allowed such procedures to be undertaken in inhibitor patients, but surgery remains uncommon because of the elevated costs of replacement therapy.

Data from 13 economic studies were recently reviewed by Stephens and colleagues [60], and it was found that the costs of rFVIIa are incurred primarily during hospitalization to manage major bleeding and facilitate orthopedic surgery (which would not have been attempted prior to the advent of rFVIIa). Interestingly, according to the studies reported in this review, the authors noted that the total cost of treating a bleeding episode with rFVIIa may be lower than that associated with using plasma-based agents. This finding that may be attributable to faster bleed resolution, higher initial efficacy rates, and avoidance of second- and third-line treatment.

According to recent observations and expert opinion on the issue of healthcare in hemophilia complicated by inhibitors, it is widely agreed that the levels of health in inhibitor patients are still not optimal. The prevention and treatment of orthopedic disability must be considered a primary goal in efforts to improve overall wellbeing and reduce treatment costs in inhibitor patients.

In 2006, Allen and Aledort reported the results of a panel discussion of therapeutic decision-making for patients with inhibitors [62]. The hematologists of the panel agreed that, when choosing treatment for each patient, there are a number of considerations to be taken into account with regard to safety, efficacy, and treatment costs. The authors of the report emphasized that treatment choice depends on an appropriate trade-off between different characteristics of the products according to such variables as patient characteristics and needs. In any case, there is still considerable uncertainty as to which therapeutic option is most appropriate in different clinical circumstances. The lack of data from comparative trials means that clinicians make the best treatment decisions possible based on their own experience, opinions and resources. Despite the best of intentions, treatment choices made in this way might not always result in provision of the best care.

The European Haemophilia Therapy Standardisation Board stated that the management of patients with inhibitors will continue to be a major challenge in hemophilia care for many years. Bypassing products are available but expensive; therefore, their use is not an option for all patients. In addition, the hemostatic effect of such agents may vary in different individuals. Consequently, comparative studies between available treatment options and analyses to predict and monitor the effect of these agents are highly warranted in order to optimize their use [65].

It is quite clear that mo consensus exists yet on the therapeutic strategy and products to use in order to improve the management of inhibitor patients. In addition, considerable uncertainty remains about the optimum treatment choice in different clinical circumstances [62, 65]. As a result, clinicians have for several years made decisions on how to manage their patients according to their own experience and opinions. These decisions can, however, differ depending on the type of patient, on the bleeding situation, and on possible considerations related to safety, immunogenicity, practicalities, product availability, and costs [49].

The management of these patients actually involves a complex interaction between different parties, i.e. physicians, patients or their caregivers, and budget holders. Each of these parties has their own set of preferences, which is influenced by the role they play in the healthcare system, their experiences, and their expectations. In order to optimise the appropriateness of the decisions, it is necessary to be both informed and aware of the opinions and preferences of the interested parties. This knowledge can be useful in order to better understand the potential benefits of treatments, thereby improving the success, and possibly also increasing the efficiency, of the intervention.

OBJECTIVE

This study was conducted with the objective of identifying and estimating the relative importance assigned to different characteristics of coagulation factor concentrates used to treat haemophilia patients with inhibitors. Preferences towards different possible coagulation factor concentrates were elicited from both patients', physicians' and pharmacists' points of view.

METHODS

Discrete Choice Analysis: technique overview

To reach the study objective, the technique of Discrete Choice Analysis (DCA) was adopted.

DCA is a technique for eliciting preferences, useful tool widely employed for estimating values of non-market goods and services. DCAs are based upon the idea that goods can be described by their characteristics (or attributes) and individuals' preferences for these goods are dependent upon the levels of the attributes.

DCAs were developed in mathematical psychology [66] and then applied in several different areas [67-71]. In the past 15 years [72] this technique has been increasingly used to elicit preferences for healthcare interventions and to allow inclusion of more than just health outcomes [73].

In the haemophilia context it was recently applied for the first time [74] and allowed to shown that process attributes such as factor infusion frequency and mode of product distribution, in addition to safety and effectiveness, are considered important in haemophilia care.

Within a DCA, hypothetical scenarios are created with combinations of previously selected attribute levels and are presented to participants who choose between a number of alternative options. As the DCA elicitation process consists of a trade-off between the attributes during the decision-making process, it has the potential to meet economic criteria for measuring benefit. Thus the technique is useful in conducting cost–benefit analyses, i.e. economic evaluations where different types of benefits can be included in one algorithm estimating the overall net benefit of alternative healthcare interventions.

DCAs make it possible to estimate whether an attribute is important, the relative importance of one attribute compared with the others, how individuals are willing to trade between different attributes, by estimating the marginal rates of substitution (MRS).

The MRS describes the rate at which individuals are willing to give up units of one "good" or of one attribute in exchange for more units of another "good" or attribute. The inclusion of "cost" as an attribute facilitates the estimation of MRS in monetary terms, known as willingness to pay (WTP), which can be interpreted as an estimate of the relative values assigned to an attribute included in the choice set, or even to a product described according to these attributes, expressed in monetary terms. By expressing the value of the attributes or products in monetary terms it is furthermore interesting as it allows to better understand the magnitude of the relative importance assigned to them because it is expressed in a unique term, which people are in general familiar with and allowing direct comparisons between different factors.

The study was conducted in four main phases: 1) study design – choosing the attributes, assigning levels to each attribute, and constructing the scenarios to be evaluated; 2) preparation of the survey instrument; 3) data collection; and 4) data analyses and interpretation of the results.

Study design

The basis for the DCA is the experimental design [75]: a Discrete Choice Experiment (DCE) is designed to obtain the scenarios that describe the potential products (or services) to be valued. A number of considerations, from both a statistical and a practical point of view were taken into account during the DCE design, with the objective of keeping a satisfying level of overall efficiency of the experiment [76], i.e. to maintain a good level of capability to

correctly and precisely capture the information of interest. The following sections describe how this study was designed.

Identification of attributes and levels

First, in order to prepare the scenarios necessary to elicit the preferences, the characteristics or attributes that describe the potential products needed to be selected, and then appropriate levels could be assigned to each attribute. In addition, both the numbers and type of attributes and levels had to be carefully selected to produce an efficient design: it is important not to select too many attributes and levels because the dimension, and hence the complexity of the experimental design, exponentially increases with these elements, which could have potentially negative effects on its capability to capture all the information of interest.

To select the attributes we organised a focus group involving physicians who are experts in haemophilia care, pharmacists with experience in this sector, and health economists. During the focus group a number of potentially interesting attributes were selected: viral safety, time to stop bleeding, possibility of undergoing major orthopaedic surgery, risk of anamnestic response, regular use in prophylaxis, time to pain recovery, number of injections to stop bleeding, and time to prepare/give/have the injection. The eight characteristics identified during the focus group were then submitted, in a pilot study [77], to 35 subjects (adult patients, paediatric patients' caregivers, physicians, pharmacists). From the results of the pilot study the seven attributes with the highest mean scores were chosen, as listed in table 1. An eighth attribute was added in order to make it possible to express preferences in terms of WTP. As the Italian National Health Service (NHS) pays for the provision of coagulation factor concentrates, it would be unrealistic to ask the respondents to imagine a patients' out of pocket payment to express their WTP for the described products.

However, citizens contribute healthcare taxes for the provision of healthcare products and services. So, in order to maintain a good level of realism in the scenarios to be presented for preferences elicitation, it was decided to ask the interviewees to imagine and to express their preferences by taking into account a hypothetical increase of their healthcare taxes, and so making it possible for inhibitor patients to receive a treatment with the described product.

After the attributes were selected, the levels for each attribute were assigned. Further focus groups of physicians with experience in the management of patients with inhibitors allowed us to select a reasonable number of interesting and realistic levels per attribute, as shown in table 1. For the "cost" attribute, the approach used for level selection was to identify plausible cost ranges for the scenarios examined during the pilot study (too low or too high levels would risk not being seriously taken into consideration by the respondent, with the possible consequences of reducing the amount and/or reliability of the responses). Participants were asked to express their WTP using additional healthcare taxes for the two possible coagulation products presented in the questionnaire. These were described according to the attributes selected during the previous focus group. The first was: a ready-to-use solution product, with viral safety as a recombinant product, requiring one infusion every other day if used in prophylaxis. One infusion was required to stop a bleeding and there was no risk of an anamnestic response when infused. The second product presented was a lyophilised material which needed to be reconstituted, and had viral safety as a plasma-derived product. It required two infusions every day if used in prophylaxis and three infusions to stop a bleeding, and had a risk of inducing an anamnestic response. After describing each product, a list of different possible costs, in terms of healthcare tax increases, was presented and the interviewees were asked to choose the amount corresponding with their maximum WTP for that product. Overall, the 35 participants in the pilot study reported, for the first product presented, an average WTP of €120 per month (from €0 to €800), while for the second product a mean of €30 per month (from €0 to €200) was estimated. In

addition, the amount of healthcare costs that Italian citizens paid in 2005 was about 8% of their income and the monthly per capita gross income was around €1700 [78-80]. Accordingly, a per capita cost for healthcare of around €130 per month was estimated. As this is compatible in its magnitude to the WTP reported by the respondents of the pilot study, it was decided to use this amount as a reference for the assignment of the levels to the cost attribute. Hence the following three levels were assigned to the "cost" attribute: 1) there is no increase in the healthcare taxes to be paid, i.e. the monthly cost remains around 8% of the per capita gross income; 2) healthcare taxes are twice those currently paid, corresponding to an increase of €130 per month to be paid by a person receiving an income of €1,700 per month; and 3) the healthcare taxes are three times those currently paid, corresponding to an increase of €260 per month to be paid from a person earning €1,700 per month.

Experimental design and choice sets generation

Every level of the selected attributes was combined in a factorial experimental design to prepare the possible product profiles (or descriptions). It must be noted that combining 2^6 X 3^2 attribute levels in a full factorial design would generate 576 possible profiles: this means that each profile obtained from this combination describes hypothetical products. The full factorial experimental design actually involves a combination of every possible profile in pair-wise choice sets, as combinations of two profiles rather than single profiles were presented to be valued: a pair-wise combination of the 576 possible profiles came to a total of 165,600 different sets to be valued. Although each respondent could value a number of sets, it would be very difficult, if not impossible, to submit this number of sets to each one. Appropriate statistical approaches were then used to extract a fractional factorial design, i.e. a restricted number of choice sets to be valued, in an attempt to keep a good level of respondents' efficiency. In order to achieve this, we aimed to not increase the burden too

much and/or difficulty of the exercise for the respondent, and to keep a good level of statistical efficiency to capture the amount of information necessary for the purposes of the study. A main-effect orthogonal fractional design containing 16 profiles, which allowed the main effects for each attribute to be estimated without correlation with each other, was selected from a catalogue [81]. In fact, we assumed that interactions among attributes were negligible, as main effects typically account for 70-90% of explained variance [82, 83]. The 16 profiles were then paired to others by applying a fold-over approach [84]. This systematic approach pairs each profile with one obtained by switching each attribute level of its comparator by one unit, to ensure that each attribute in each choice set maintained a minimum overlap: this implies that the respondents make choices by evaluating every attribute. Sixteen pair-wise choice sets were finally produced. According to literature on the application of DCAs [72] and previous experience in the haemophilia context [74] we considered this a reasonable number of choice sets to be submitted to each respondent.

Study sample

In order to obtain preferences from the different points of view relevant for the topic of the study, the following individuals were involved: patients with inhibitors or their caregivers (one parent or guardian), physicians who are specialists in haemophilia care, and pharmacists with experience in managing and delivering coagulation factor products. We contacted and invited the physicians and pharmacists to participate in the study. Physicians were also asked to enrol patients, or their parents/guardians, if the patients were younger than 17 years of age. In particular, patients of any age with inhibitors or their parents/guardians, who were able to understand the scope of the study and their task and who were willing to participate, were enrolled in the study. Parents/guardians were interviewed in the case of paediatric patients: in fact, if the patients were aged less than 17 years one of their caregivers

was asked to complete the questionnaire and express their own preferences. Each patient or parent/guardian was asked to sign an informed consent for his/her participation.

Ethical issues

This study was conducted in accordance with the principles from the 18th World Medical Assembly [85] and all subsequent amendments. Approval for the study was given by the Ethical Committee of the coordinating centre, the A. Bianchi Bonomi Haemophilia and Thrombosis Centre of the IRCSS Foundation Policlinico, Mangiagalli and Regina Elena Hospitals.

Survey instrument and data collection

The participants self-completed a questionnaire at enrolment. The questionnaire included an explanation sheet clarifying the scope of the interview and instructions on how to complete the task. Specifically, the meaning of each attribute and its levels were explained to the participants. They were then invited to imagine, at each choice set (for a total of 16 choice sets), that they had at their disposal two options of coagulation factor concentrates, described according to the reported attribute levels. The participants' task was to evaluate the two options in each choice set and to choose the one option that globally reached the maximum value from their point of view. An example of a scenario and choice question is shown in figure 1. Information on socio-demographics, on clinical data (e.g. presence of viral infections, peak and last inhibitor titre, frequency of haemorrhages, and occurrence of surgery in the previous 4 months), on the type of treatment regimen, and on the product used, was requested. Physicians and pharmacists were asked to specify their experience with inhibitor patients and/or products used in inhibitor patients.

Data analyses

DCAs are based on Lancaster's economic theory of value [86] and on the assumption of utility maximization behaviour by the decision-maker, in line with the Random Utility Theory (RUT) [87-89]. According to the RUT framework, utility can be separated into a systematic or explainable component and a random component:

$$U_{ij} = V_{ij} + \varepsilon_{ij}$$

where U_{ij} is the utility derived from choice j by the individual i, V is the systematic, measurable component of utility, and ε is the random error, attributable to the component of utility that the researcher cannot observe. The assumption is that individual i chooses alternative j if the utility derived from that alternative is greater than the utility derived from any other alternative k in the choice set ($U_{ij} > U_{ik}$).

To analyse the data, a logistic regression model was applied to the difference between the levels of each attribute. Furthermore, in order to take into account the error component attributable to the variability among the respondents, i.e. those who provided multiple observations, a random effects model was applied [88].

The following linear additive functional form for the systematic component of the utility function was assumed:

$$Vj - Vk = \triangle V = \beta_1 * \triangle INFECTION + \beta_2 * \triangle TITRE + \beta_3 * \triangle INFUS\_BLEED +$$

$$+ \beta_4 * \triangle TIME\_BLEED + \beta_5 * \triangle TIME\_PAIN + \beta_6 * \triangle INFUS\_PROF + \beta_7 * \triangle SURGERY +$$

$$+ \beta_8 * \triangle COST$$

where $\triangle V$ is the change in utility in moving from option B (having Vj) to A (with Vk): a difference model was in fact estimated and the independent variables included in the model were actually the differences between levels of each attribute (as specified with "$\triangle$"); hence, the coefficients (corresponding to the estimates of β) reported in the results section must be interpreted as for differences between each attribute level: in other words $\beta_{1\text{-}8}$ represent the taste weights of one unit level of change of the corresponding attribute, i.e. the relative importance of each attribute on choice. It is important to be aware of the unit of measurement. For instance β_1 indicates the value (taste weight) given to having a product with a perceived viral risk from a recombinant product over one with a risk from a plasma-derived product; β_3 indicates the mean value given to reducing by 1, within the range of 1 to 3, the number of infusions necessary to stop the bleeding, and β_8 is the mean value given to each € within the range from 0 to 260 to be paid as additional healthcare taxes.

The sign of the parameter estimates was observed to verify if the direction of the preferences corresponded to the expected one: a priori it was hypothesised that a risk of viral infection from a recombinant product is perceived to be lower, and hence would be preferred to the risk of a plasma-derived one. A negatively signed regression coefficient was therefore expected, according to the codes included in the model, as reported in table 1. Similarly, parameter estimates regarding the risk of anamnestic response, the number of infusions to stop bleeding, the time to stop the bleeding after the infusion, the time for pain recovery, the frequency of weekly infusions in the case of prophylaxis treatment, and the cost were

expected to have a positive sign. Finally, the parameter for the possibility of undergoing major surgery was expected to have a negative sign.

The MRS between two attributes was estimated in terms of WTP by dividing each parameter estimate by the estimate for the cost attribute: these estimates show how much of one attribute respondents would be willing to pay for, in terms of healthcare taxes (parameter estimate for the cost attribute at the denominator), to have an improvement of another attribute (at the numerator).

In order to understand which attribute contributes more to the utility of the drugs under study, their relative importance (RI) was estimated by computing the ratio of the utility given to each attribute, within the range of the levels assigned, to the sum of the utilities assigned to the level ranges of all the attributes included in the experiment.

All the analyses were conducted by splitting the sample into three subgroups, in order to identify and investigate the different preferences between the points of view of the patients (or their caregivers), the physicians, and the pharmacists.

Although discrete choice exercises imply that people make trade-offs between the submitted attributes according to their different levels, this does not always happen. In fact, in some cases the respondent shows apparent unwillingness to accept reductions in one attribute in return for improvements in others, exhibiting the so-called lexicographic preferences with respect to the attribute he/she prefers. In this case the respondent always chooses that attribute in every choice set presented, without trading between the other ones. We tested also whether lexicographic preferences were present among the participants in this study.

The results of the analyses were considered statistically significant if p<0.05, with two-tailed tests. Analyses were conducted with STATA version 9.0 and with SPSS version 15.0.

RESULTS

Description of the study sample

A total of 101 people were enrolled and interviewed from different regions of Italy: 25 adult patients, 12 paediatric patients' caregivers, 39 physicians, and 25 pharmacists.

Both adults and caregivers of paediatric patients were enrolled in the study. A full description of the characteristics of the patients is reported in table 2.

Twenty-one (84%) pharmacists had experience in preparing and/or dispensing coagulation factor concentrates for patients with inhibitors. Thirty-four physicians (87%) had experience in prescribing and/or preparing and/or administrating coagulation factor concentrates for patients with inhibitors.

Preferences towards coagulation factor concentrate characteristics

A total of 1614 observations (choices) were obtained from the discrete choice exercises. Only two out of 101 respondents skipped one of the 16 choice sets submitted, with a response rate of 99.9%. The high response rate suggests a good level of feasibility of the exercises submitted to the interviewees.

Table 3 presents the regression results from the overall sample. According to the coefficient signs the theoretical validity of the model was confirmed. In particular, the respondents preferred a product with a level of safety from risk of viral infection as the one attributed to a recombinant product, when compared with a product with viral safety as the one assigned to a plasma-derived product. They preferred a product with no risk for the

inhibitor titres increasing, that requires a lower number of infusions, a lower time to stop bleeding after the infusions, a lower time to pain recovery, a lower number of infusions per week in case it is used prophylactically, that allows the patient to undergo major surgery, and has a lower cost in terms of additional healthcare taxes. The statistical significance of the parameter estimates (p=0.006 in the regression coefficient for frequency of infusions in prophylaxis regimen, p<0.0001 in every other attribute) show that every attribute included in the scenarios is important to the interviewees.

When looking at the results from each subgroup of respondents, i.e. the patients or their caregivers, the physicians, and the pharmacists, the data show that the direction of preferences did not change among these subgroups; however, the relative importance assigned to some attributes was different, as shown in table 4 and in more detail in figure 2. Three attributes, namely time to stop the bleeding, possibility of undergoing major surgery, and cost were found to be statistically significant by every subgroup. Figure 2 shows the impact of each attribute, within the range of levels included, relative to the importance of all the attributes included in the scenarios. As a point of reference, the RI would be 100/8 = 12.5% if all eight attributes were of equal importance.

For patients (or their caregivers) the most important factors affecting treatment decision were: increase in healthcare taxes (RI=21.0%), risk of anamnestic response (RI=20.3%), the possibility of undergoing major surgery (RI=17.9%), and perceived viral safety (RI=17.7%). For physicians the most important factors were: increase in healthcare taxes (RI=25.7%), risk of anamnestic response (RI=18.2%), number of infusions to stop bleeding (RI=14.2%), and the possibility of undergoing major surgery (RI=13.2%). For the pharmacists the most important factors were: increase in healthcare taxes (RI=26.8%), time

to stop bleeding (RI=19.8%), time to pain recovery (RI=14.4%), and the possibility of undergoing major surgery (RI=13.4%).

It is particularly interesting to note that every subgroup assigned the highest relative value to the increase of healthcare taxes. Another very interesting finding is the high value given by the patients/caregivers and physicians to the risk of anamnestic response, in contrast with the pharmacists' opinion, and the high value attributed to the perceived viral safety given by the patients/caregivers, followed by the pharmacists, but not by the physicians.

It is also worth noting that 16 respondents (five adult patients, five caregivers, three physicians, and three pharmacists) showed a non-trading attitude toward some characteristics, i.e. they made their choices by always taking into account the same attribute and skipping a trade-off between the attributes included in the scenario. In particular three physicians, two patients, and two caregivers always preferred the option with no risk of anamnestic response; six patients and one pharmacist always chose according to the product's viral safety. One pharmacist always chose the options allowing the patient to undergo surgery, while another pharmacist always chose the products requiring 12 instead of 24 hours to stop the bleeding after infusion.

Willingness to Pay

The different relative values given by the three categories of respondents to each characteristic corresponded to different WTPs, as shown in Table 4. In particular, the patients/caregivers and the physicians would on average be willing to accept an increase of taxes up to €260 and €200 per month, respectively (by assuming a monthly gross income of €1,700), to make available a product with no risk of anamnestic response, assuming all other

things were equal. Pharmacists would on average be willing to pay around €20 per month. The patients/caregivers would pay up to €229 for a product allowing patients to undergo major (e.g. orthopaedic) surgery, the physicians €145, while the pharmacists would on average pay €115 per month. Regarding the perceived viral safety, the patients/caregivers and pharmacists would be willing to accept an increase of taxes up to €226 and €107, respectively, while the physicians would on average pay around €33 per month to have a recombinant versus a plasma-derived product. The patients/caregivers and the pharmacists would on average pay up to €15 extra per month for a product that reduced the time to stop a bleed by one hour, while the physicians would pay around €10 per month. The patients/caregivers would be willing to pay €90 extra per month to have a product requiring one infusion every other day instead of one requiring one infusion every day; however, the physicians would pay €48 and the pharmacists €26 per month. While the physicians and pharmacists would pay €31 per month for a product that reduced time to pain recovery by 1 hour, the patients showed a lower WTP for this attribute, corresponding to €7 per month in additional healthcare taxes. Finally, while the physicians would pay €78 per month for a product requiring one infusion less to stop the bleeding, the pharmacists would pay €34 and the patients/caregivers would pay just €1 per month.

DISCUSSION

Summary of results and main potential implications

To our knowledge this is the first work comparing the value given by patients (or their caregivers), physicians, and pharmacists to the different characteristics of coagulation factor concentrates used for the treatment of haemophilia patients with inhibitors. Not only outcome attributes (i.e. viral safety, risk of anamnestic response, the time to stop a bleeding, time to alleviate the pain, and possibility of undergoing major surgery), but also process attributes (frequency of infusions to stop a bleeding or to follow a prophylaxis regimen) and cost are considered important for a product used in patients with inhibitors. Cost, in terms of additional healthcare taxes, was the most important attribute to every group. However, high monetary values were added to a number of characteristics, above all to the risk of anamnestic response by patients/caregivers and physicians; to the possibility of undergoing surgery by every respondent group; and to the viral safety assigned to the products by the patients/caregivers and the pharmacists.

Historically, the objective of hemophilia treatment was to survive the disease; however, hemophilia is no longer considered to be a life-threatening condition, as advanced health technologies have improved patients' life expectancy [90] and allowed to keep relatively good levels of HRQoL [e.g., 49, 53, 57]. Nonetheless, much work is still necessary to optimize patients' health, but on the other hand there is still considerable uncertainty regarding the issue of which therapeutic strategy provides optimal benefit. Among the most crucial issues to be considered, resource constraints often limit access to the most effective treatment options. In an era of limited resources competing with potentially unlimited needs and demands, it is necessary to make decisions on how, where and for whom to allocate these resources.

Appropriate investments must be identified and applied if we are to achieve efficient management of hemophilia patients. Investments incur cost and can be perceived as too expensive, at least in the short-term; however, appropriate investments should be considered as opportunities to improve patients' overall health and wellbeing. Furthermore, implementation of appropriate investments could also translate into economic benefits from the perspective of patients, their carers, the healthcare system, and society as a whole. In order to make rational decisions about which treatment strategies to apply, the costs associated with such treatments should be considered together with the benefits they allow and the potential benefits that may be lost if they are not used.

Taking into considerations these several and different aspects also depend on decision makers' opinions and preferences, which depend on different factors, not always or only attributable to clinical issues. Some opinions are inherent to the products or services themselves, but others are related to other aspects, such as patients' needs, experiences and expectations. In haemophilia care, unlike those in some other contexts, preferences from different actors, including patients, occupy a primary role in the decision-making process.

Against some expectancies, economic issues are considered important as well by people involved in haemophilia: this study in fact showed that although the treatment for haemophilia is paid for by the Italian NHS, every group of respondents showed awareness of the potential cost to them that a product could generate.

The results of this study are relatively comparable with those of another recently published study [91]. The focus of the Lee study was only on physicians' preferences: according to a group of US specialist physicians, 64% of the relative importance was given to the time and number of infusions required to stop bleeding, the time required to alleviate pain, the anamnestic response, and the risk of viral infections. Except for the perceived risk of viral infections, these attributes are also among the most important attributes in the present study. Interestingly, the cost of medication was one of the lowest important characteristics in

the Lee study. Differences in the results of the two studies may be explained by a number of reasons. One possible reason is attributable to the different scenarios presented to the participants, with different characteristics and different levels assigned to each characteristic: for instance, the cost attribute was expressed in a completely incomparable way in the two studies. With this in mind, it must be noted that the options proposed in the two studies were the result of previous research conducted to construct the scenarios according to their potential interest and realism in the target context. For instance, the choice to consider healthcare taxes as a proxy for the cost attribute may not be directly applicable in some countries, e.g., those that have a private insurance system to finance healthcare. Other differences in the results could also be due to the differing experiences of physicians in their countries. In considering these factors, we believe that the key information from the study regarding the relative value given to characteristics of each product used to treat inhibitor patients, from the different people involved, are valid and reliable for other healthcare systems where the study population is similar to this one.

A large number of considerations have to be taken into account when choosing the treatment for each patient. They are based on safety, effectiveness, costs, experiences and opinions. According to a panel of haematologists who discussed treatment choices for inhibitor patients [62]. They specified that a trade-off between different characteristics of the products or treatment regimen is necessary when choosing the strategy to be adopted. However, a lack of consensus exists on the most appropriate therapeutic strategy to be adopted, while economic issues can be the cause of barriers for the application of the most appropriate therapeutic options [58-65] . Increasing the knowledge and awareness of the preferences of the different parties in the decision-making process, i.e. physicians, budget holders, as well as patients or their carers, is a primary objective that should be pursued to improve the benefits of the treatment. The results of the present study can help to reach this

objective, in particular, the information provided by this work can be useful for optimal decision making, when taken into account with other factors based on safety, clinical effectiveness, patients' quality of life, and costs. A comprehensive evaluation of all of these components can allow the overall value of the different treatment options to be recognised, and so facilitate the identification of the most appropriate treatment for each situation.

Study limitations

Some potential limits can be ascribed to this study. First, 36% of the respondents showed a non-trading attitude, i.e. they always chose according to the same characteristic, giving up a possible trade-off between the other ones. Although this attitude can be attributed to a real unwillingness to trade between attributes, i.e. a very strong preference toward only one attribute, "at any cost", another reason for this phenomenon could be ascribed to the complexity of the exercises. It has been suggested that the more complex a choice becomes in terms of the number of options and the variability within options, the less likely people are to engage in compensatory decision making and instead adopt a lexicographic ordering of attributes [92]. We were aware of the possible difficulties that can be encountered during the completion of a discrete choice exercise and during the design paid special attention to this aspect. For example, in order to improve the efficiency of the design [76] and to reduce the burden of the exercise, we selected the number and type of both attributes and levels per attribute that would make the scenarios as feasible, acceptable, realistic, and interesting as possible.

Some criticisms may arise because of the decision to estimate the monetary values assigned to the attributes of a coagulation factor concentrate, which could be considered unrealistic, and therefore not appropriate within the context examined. The approach of WTP is in fact not simple to apply. One reason for this is that neither the patients, nor the

physicians or the pharmacists actually pay for the provision of coagulation factor concentrates, because in the Italian healthcare system the NHS completely covers the cost of these products. However, allowances were made for this during the design of this study, as specified in the methods section. Furthermore, the subjects participating in the study assigned a high relative importance to the possibility of having to pay higher healthcare taxes. However, they also showed a willingness to pay higher taxes so that better coagulation factor concentrates could be available to inhibitor patients.

Finally, some criticisms may be attributed to the size of the sample. It is, however, important to note that the number of patients or caregivers (37), physicians (39), and pharmacists (25) should actually be considered relatively big, if framed within the target population, which in Italy comprises around 300 patients. Furthermore, it is important to note that every participant contributed 16 observations each (i.e. 16 choices), to a total of more than 1600 observations.

Conclusion and considerations for future investments

Inhibitors constitute a potentially serious obstacle to haemophilia treatment. Strategies like the implementation of ITI or the use of bypassing agents has proved successful, but this has been achieved through apparently very costly investments. However, the cost of these investments must be considered together with the benefits they actually bring – benefits that can depend not only on the characteristics of the patients, but also on their preferences, expectations, and on opinions and experiences of the other parties involved in the decision-making.

The present study enabled us to estimate the relative importance and magnitude of value assigned to the different characteristics of coagulation factor concentrates according to different points of view.

Taking into consideration knowledge on these preferences, together with other aspects like the patients' clinical needs, can help to optimise decisions on the use of different products (e.g. rFVIIa versus aPCC) and treatment regimens (e.g. prophylaxis versus on-demand) in this challenging patient population.

Next efforts to be done by the health care systems, to optimally manage people with haemophilia, must focus on reducing the consequences attributable to the disease in order to improve patients' health. Reducing the costs of managing hemorrhages and arthropathy, performing surgery and satisfying other clinical needs should be considered a further objective. Decision-making in hemophilia care involves a complex interaction between different parties, i.e. physicians, patients, and budget holders, each of which carries their own set of needs (e.g. patients' clinical status; treatment costs), experiences, expectations, and preferences, all influenced by the role that these parties play in the healthcare system []. In order to allow for appropriate decisions, every relevant aspect must be analyzed.

For instance, prophylaxis is recognized for its potential benefits in terms of bleeding reduction, prevention of future disabilities, and consequent improvement of patients' health and wellbeing. Subsequently, further benefits could also be expected from both the patients' and society's point of view, as a reduction in the costs of managing complications and productivity could be expected. Prophylaxis can be a particularly challenging regimen, and might not be applicable to all inhibitor patients [58] In addition, prophylaxis appears to be very expensive, at least in the short term. Information on both present and future costs and benefits (from the perspective of patients, their carers and the healthcare system), is thus

necessary to understand the relative value of the compared options and then to make rational decisions on which one to apply.

Hemophilia is a chronic, lifelong condition. The management of this disease and related consequences should be considered as a long-term investment; present and future benefits and associated costs should all be taken into account when evaluating and comparing treatment options. Generally speaking, making investments incurs costs, with the precise objective of gaining benefits. Not making investments can apparently incur less or no cost; however, questions should be asked about the consequences that can be expected from not making investments, in terms of present and future benefits and costs.

Conducting appropriate health technology evaluations, including both clinical and economic issues, is strongly encouraged in order to gain all the information necessary for making decisions that lead to efficient investments.

Economic evaluations are techniques applied to estimate and compare benefits and costs derived from the application of alternative options, with the objective of informing decision-makers about the most efficient one and hence contributing to appropriate decisions.

Health economics, which involves the application of the principles and concepts of economics [93] to the healthcare sector, is therefore an aid to decision-making for healthcare interventions; it is not aimed at containing costs, but rather at rationalizing the allocation of the available resources to maximize the benefits derived from their use. Furthermore, the application of economic principles to the evaluation of healthcare interventions is complementary – not an alternative – to the assessment of their quality, safety and effectiveness.

TABLES AND FIGURES

Table 1: Attributes and levels description

Attributes (labels)	Levels: codes (as included in the model) and description
Perceived risk of viral infection (INFECTION)	(0) As from a plasma-derived product (1) As from a recombinant product
Risk of anamnestic response (TITRE)	(0) No (1) Yes
Number of infusions to stop bleeding (INFUS_BLEED)	(1) 1 infusion (2) 2 infusions (3) 3 infusions
Time to stop bleeding (TIME_BLEED)	(12) 12 hours (24) 24 hours
Time to pain recovery (TIME_PAIN)	(2) 2 hours (6) 6 hours
Number of weekly infusions if used in prophylaxis regimen (INFUS_PROPHY)	(0) 1 infusion every other day (1) 1 infusion every day
Possibility of undergoing major surgery (SURGERY)	(0) No (1) Yes
Increase of healthcare taxes (COST)	(0) No additional contribution in healthcare taxes required (130) Having to pay double the current taxes, i.e. €130 more assuming a monthly gross income of €1,700 (260) Having to pay triple the current taxes, i.e. €260 more assuming a monthly gross income of €1,700

Explanation of the meaning of each attribute: INFECTION refers to viral risk of infection as that perceived from a highly purified plasma-derived concentrate versus a risk as perceived from a recombinant product; TITRE refers to the presence versus absence of possibility for the titre of inhibitors to increase after the infusion; INFUS_BLEED refers to the number of infusions necessary to stop a bleeding; TIME_BLEED refers to the time necessary to stop a bleeding after the infusion; TIME_PAIN refers to the time necessary to stop pain; INFUS_PROF refers to the number of necessary infusions in a prophylactic regimen; SURGERY refers to the possibility of undergoing a major intervention, like joint implantation, versus not having this possibility. Finally COST refers to the increase in healthcare taxes to the Italian citizens in order for inhibitor patients to be able to receive the products described.

Table 2: Description of the patients

Description		Adult patients (N=25)	Paediatric patients (N=12)
Age: mean (SD)		41.4 (11.0)	8.2 (4.6)
(median; min-max)		(39.9;17.0-62.0)	(7.7; 2.0-16.0)
Patients with severe haemophilia A: N (%)		25 (100)	12 (100)
Patients with viral infections: N(%)			
Hepatitis C infection		21 (84.0)	0.0
Hepatitis B infection		4 (16.0)	0.0
HIV		4 (16.0)	0.0
Inhibitors titre (BU/mL):			
Historical peak titre	mean (SD)	1,040.0 (2,642.0)	1,040.0 (2,642.0)
	median (min-max)	164.0 (5.0-13,000.0)	167.5 (6.0-16,400.0)
Last recorded titre:	mean (SD)	85.0 (206.0)	67.6 (150.4)
	median (min-max)	10.0 (0.0*-800.0)	15.0 (1.0-516.0)
Patients with haemorrhages 4 months before the interview N (%):	0	2 (8.0)	2 (16.7)
	1-2	8 (32.0)	2 (16.7)
	3.5	7 (28.0)	2 (16.7)
	≥ 6	8 (32.0)	6 (50.0)
Patients undergoing surgery in the previous 4 months N(%)		3# (12.0)	0
Treatment regimen followed at the time of the interview: N (%) of patients			
Prophylaxis		5 (20.0)	2 (16.7)
Immunotolerance		4 (16.0)	5 (41.7)
On demand		16 (64.0)	5 (41.7)
Coagulation factor used in the 4 months before the interview: N (%) of patients			
rFVIIa		15 (60.0)	8 (66.7)
aPCC		10 (40.0)	4 (33.3)
Recombinant FVIII		1 (4.0)	5 (41.7)
Plasma-derived FVIII		5 (20.0)	0
Patients using more than one product: N (%)		5 (20.0)	5 (41.7)

* Although these patients had no inhibitors according to the last detection before the interview they were acknowledged and treated as inhibitor patients.

1 patient underwent ankle arthroscopy, 1 underwent arthrocentesis, and 1 underwent surgery for scrotal-inguinal hernia

Table 3: Results of the main model, showing the results from the whole sample

Attribute	Coefficients (β estimates)° and Standard Errors	P values
INFECTION	-0.334 (0.060)	0.000
TITRE	0.526 (0.057)	0.000
INFUS_BLEED	0.154 (0.044)	0.000
TIME_BLEEDS	0.038 (0.005)	0.000
TIME_PAIN	0.081 (0.015)	0.000
INFUS_PROPHY	0.159 (0.057)	0.006
SURGERY	-0.515 (0.061)	0.000
COST	0.003 (0.000)	0.000

Number of observations	1614
Number of subjects	101
Rho	0.006
Log Likelihood#	-932.564
McFadden R^{2} *	0.1669
Chi-square (p value)	297.13 (<0.0001)

° Coefficients are computed for the difference between the levels of each attribute. For instance, the coefficient of "INFECTION" represents the taste weight for moving from a recombinant to a plasma-derived product, every other attribute assumed to be equal. Regarding domains coded as continuous variables (INFUS_BLEED, TIME_BLEED, TIME_PAIN, COST), the coefficient represents the taste weight for one unit of change in the corresponding attribute level.

The sign indicates the direction of preferences: in case of "INFECTION" the negative sign means that respondents preferred recombinant (coded as 1) over plasma-derived products (coded as 0); regarding COST, the positive sign of coefficients means that respondents preferred lower over higher cost. # Logistic regression uses maximum likelihood approach to estimate parameters

* Pseudo R^{2} (McFadden R^{2}) is a measure of the overall model goodness-of-fit. It is defined as $1-(LL/LL_{0})$, where LL is the value of the log-likelihood function evaluated at the estimated parameters, LL_{0} is the value of the log-likelihood function for a base model that only contains the intercept (constant)

Table 4: Results of the segmentation model, showing the results from each sub-sample

Attribute	Patients and caregivers		Physicians		Pharmacists	
	Coefficients° (p values)	WTP (95% CI)	Coefficients° (p values)	WTP (95% CI)	Coefficients° (p values)	WTP (95% CI)
INFECTION	-0.439(0.000)	**226.37** (88.56, 364.17)	-0.151 (0.161)	**32.77** (-12.97, 78.51)	-0.482(0.000)	**107.24** (53.11, 161.38)
TITRE	0.503 (0.000)	**259.80** (81.08, 438.51)	0.919 (0.000)	**199.67** (128.98, 270.35)	0.085 (0.484)	**18.80** (-36.16, 73.76)
INFUS_BLEED	0.002(0.971)	**1.26** (-67.49, 70.01)	0.359 (0.000)	**77.92** (39.93, 115.91)	0.154 (0.120)	**34.41** (-7.64, 76.47)
TIME_BLEED	0.028 (0.000)	**14.57** (4.40, 24.73)	0.042 (0.000)	**9.07** (5.23, 12.90)	0.064 (0.000)	**14.13** (9.02, 19.25)
TIME_PAIN	0.014(0.562)	**7.14** (-18.66, 32.94)	0.142 (0.000)	**30.84** (15.45, 46.23)	0.139 (0.000)	**30.89** (13.31, 48.47)
INFUS_PROPHY	0.174(0.055)	**90.01** (-11.60, 191.62)	0.221 (0.036)	**48.02** (2.16, 93.88)	0.117 (0.330)	**26.05** (-26.19, 78.30)
SURGERY	-0.444(0.000)	**229.27** (82.70, 375.85)	-0.669 (0.000)	**145.47** (89.86, 201.08)	0.518 (0.000)	**115.26** (53.66, 176.87)
COST	0.002(0.000)	/	0.005 (0.000)	/	0.004 (0.000)	/

No. of observations	1614
Number of subjects	101
Rho	0.006
Log Likelihood#	-892.085
McFadden R^{2} *	0.202
Chi-square (p value)	303.93 (p<0.0001)

° Coefficients are computed for the difference between the levels of each attribute. For instance, the coefficient of "INFECTION" represents the taste weight for moving from a recombinant to a plasma-derived product, every other attribute assumed to be equal. Regarding domains coded as continuous variables (INFUS_BLEED, TIME_BLEED, TIME_PAIN, COST), the coefficient represents the taste weight for one unit of change in the corresponding attribute level. The sign indicates the direction of preferences: in case of "INFECTION" the negative sign means that respondents preferred recombinant (coded as 1) over plasma-derived products (coded as 0); regarding COST, the positive sign of coefficients means that respondents preferred lower over higher cost.
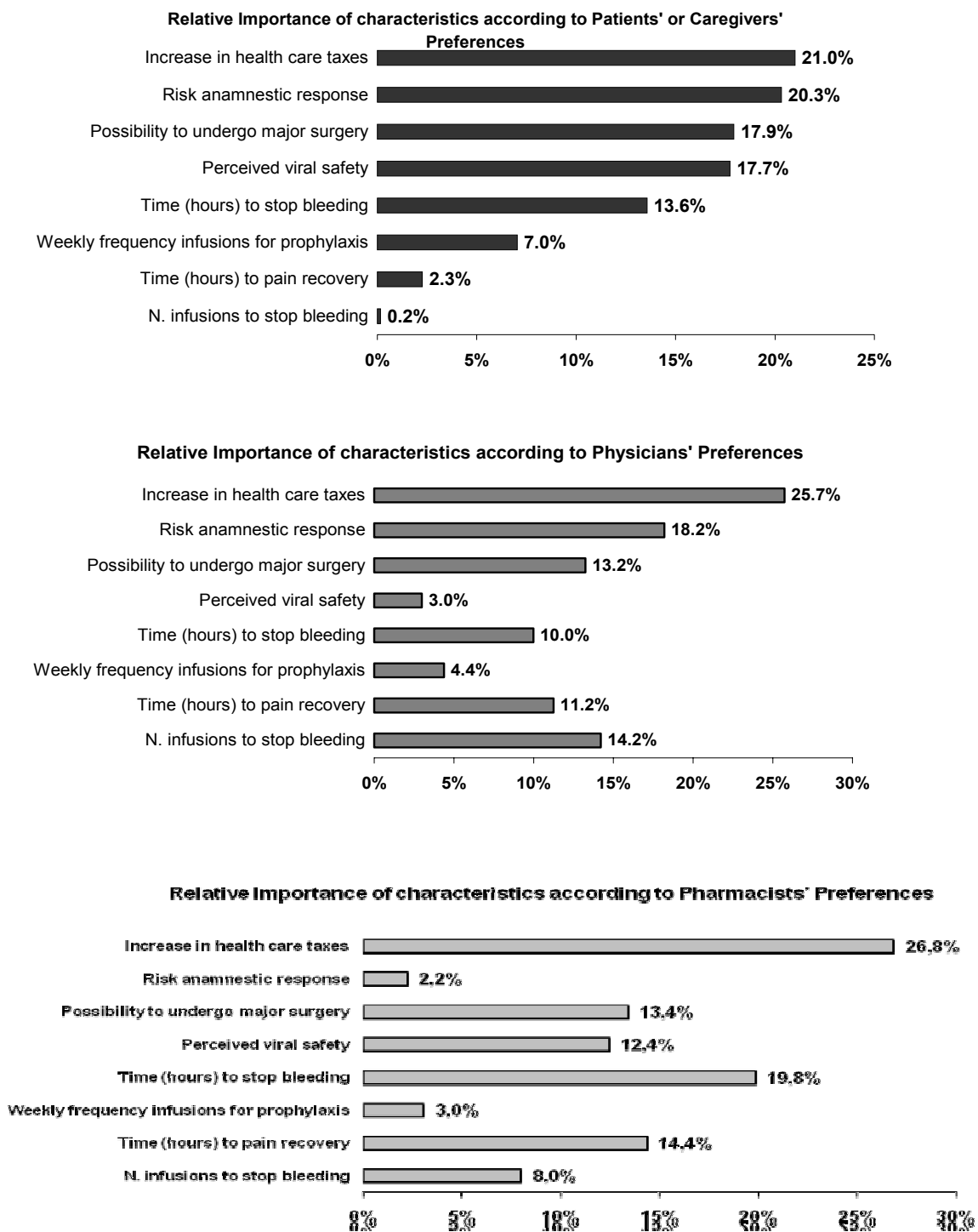
Logistic regression uses maximum likelihood approach to estimate parameters

* Pseudo R^2 (McFadden R^2) is a measure of the overall model goodness-of-fit. It is defined as 1-(LL/LL_0), where LL is the value of the log-likelihood function evaluated at the estimated parameters, LL_0 is the value of the log-likelihood function for a base model that only contains the intercept (constant)

Figure 1: Example of a choice set presented to the respondents

ATTRIBUTES	TREATMENT A	TREATMENT B
Perceived risk of viral infection	As a plasma-derived concentrate	As a recombinant factor concentrate
Risk of anamnestic response	Yes	No
Number of infusions to stop bleeding	1 infusion	2 infusions
Time to stop bleeding	12 hours	24 hours
Time to pain recovery	2 hours	6 hours
No of weekly infusions if used in prophylaxis	1 infusion every other day	1 infusion every day
Possibility of undergoing major surgery	No	Yes
Healthcare taxes increase	None	Doubling health care taxes
Which product would you choose, A or B?	A ☐	B ☐

Figure 2: Relative importance assigned by each sub-group of respondents to each attribute.

Relative Importance of characteristics according to Patients' or Caregivers' Preferences

Attribute	Value
Increase in health care taxes	21.0%
Risk anamnestic response	20.3%
Possibility to undergo major surgery	17.9%
Perceived viral safety	17.7%
Time (hours) to stop bleeding	13.6%
Weekly frequency infusions for prophylaxis	7.0%
Time (hours) to pain recovery	2.3%
N. infusions to stop bleeding	0.2%

Relative Importance of characteristics according to Physicians' Preferences

Attribute	Value
Increase in health care taxes	25.7%
Risk anamnestic response	18.2%
Possibility to undergo major surgery	13.2%
Perceived viral safety	3.0%
Time (hours) to stop bleeding	10.0%
Weekly frequency infusions for prophylaxis	4.4%
Time (hours) to pain recovery	11.2%
N. infusions to stop bleeding	14.2%

Relative Importance of characteristics according to Pharmacists' Preferences

Attribute	Value
Increase in health care taxes	26.8%
Risk anamnestic response	2.2%
Possibility to undergo major surgery	13.4%
Perceived viral safety	12.4%
Time (hours) to stop bleeding	19.8%
Weekly frequency infusions for prophylaxis	3.0%
Time (hours) to pain recovery	14.4%
N. infusions to stop bleeding	8.0%

45

ACKNOWLEDGEMENTS

A paper on this study has been recently accepted for publication in Haemophilia Journal:

L Scalone, LG Mantovani, F Borghetti, S von Mackensen, A Gringeri: Patients', Physicians', and Pharmacists' Preferences towards Coagulation Factor Concentrates to Treat Haemophilia with Inhibitors: Results from the COHIBA Study. Haemophilia – IN PRESS

Further papers related to this study are:

L Scalone. Investing in hemophilia care: benefits and costs for patients and society. Seminars in Hematology, 2008; 45: S31-S34

Paul FM Krabbe, Luciana Scalone. Probabilistic Choice Models in Health Evaluation Research: Background, Theories & Assumptions. *Under review for publication in Social Science and Medicine*

REFERENCES

1. Ghirardini A, Schinaia N, Chiarotti F, De Biasi R, Rodeghiero F, Binkin N, Gruppo italiano coagulopatie congenite. Epidemiology of hemophilia and of HIV infection in Italy. J Clin Epidemiol 1994;47:1297-1306.

2. Prevention and control of haemophilia: memorandum from a joint WHO/WFH meeting. Bulletin of the World Health Organization 1991, LXIX, 1, 17-26.

3. Soucie JM, Evatt B, Jackson D. Occurrence of hemophilia in the United States. The Hemophilia Surveillance System Project Investigators. Am J Hematol; 59(4):288-94.

4. Trimestra AHM, Smit C, Van der Ploeg HM, Briet E, Rosendal FR. Two decades of haemophilia treatment in the Netherlands, 1972-1992. Haemophilia 1995;1:165-171.

5. Miners AH, Sabin CA, Stevens AJ, Tolley KH, Lee CA. Financing the rising cost of haemophilia care at a large comprehensive centre. Journal of the Royal College of Physicians of London, 1997; 31: 640-644.

6. Barr RD, Saleh M, Furlong W, Horsman J, Sek J, Pai M, Walker I. Health status and health-related quality of life associated with hemophilia. Am J Hematol 2002;71(3):152-60.

7. Lawrence JS, Johnson JB. The presence of a circulating anti-coagulant in a male member of a haemophiliac family. Trans Am Clin Climatol Assoc, 1941; 57: 223-231

8. Astermark J. Overview of Inhibitors. Seminars in Hematology, 2006; 43: S3-S7

9. Wight J, Paisley S. The epidemiology of inhibitors in haemophilia A. a systematic review. Haemophilia, 2003; 9: 418-435

10. DiMichele D. Inhibitors: resolving diagnostic and therapeutic dilemmas. Haemophilia 2002; 8: 280–3.

11. Katz J. Prevalence of factor IX inhibitors among patients with hemophilia B; results of a large scale North American Survey. Haemophilia, 1996; 2: 28-31

12. Ehrenforth S, Kreuz W, Scharrer I et al. Incidence of development of factor VIII and factor IX inhibitors in haemophiliacs. Lancet 1992;339:594-598.

13 Kreuz W. Escuriola-Ettinghausen C, Martinez-Saguer I, Güngör T, Kornhuber B: Epidemiology of inhibitors in hemophilia. A.Vox Sang 1996;70(suppl 1):2

14. Kulkarni R, Aledort LM, Berntorp E, Brackman HH, Brown D, Cohen AR, Ewing NP, Gringeri A, Gruppo R, Hoots K, Leissenger C, Peerlinck K, Poon MC, Wong WY. Therapeutic choices for patients with hemophilia and high-titer inhibitors. Am J Hematol 2001;67(4):240-6

15. Ingerslev J. Hemophilia. Strategies for the treatment of inhibitor patients. Haematologica 2000;85(10 Suppl):15-20

16. DiMichele DM, Kroner Bl. North American Immune Tolerance Study Group. The North American Immune Tolerance Registry: practices, outcomes, outcome predictors. Thromb Haemost, 2002; 87: 52-57

17. DiMichele DM. Inhibitors in haemophilia: a primer. Haemophilia 2000; 6: 38–40.

18. Oldenburg J, Tuddenham E. Inhibitor to factor VIII – molecular basis. In: Lee CA, Berntorp EE, Hoots Wk, eds. Textbook of Hemophilia. Malden, MA: Blackwell Publishing Ltd, 2005: 59-63

19. Santagostino E, Mancuso ME, Rocino et al. Environmental risk factors for inhibitor development in children with haemophilia A: a case-control study. Br J Haematol 2005; 130: 422-7

20. Lorenzo JI, Lopez A, Altisent C, Aznar JA. Incidence of factor VIII inhibitors in severe haemophilia: the importance of age. Br J Haematol 2001; 113: 600-603; Van der Bom JG, Mauser-Bunschoten EP, Fischer K, van der Berg HM. Age at first treatment and immune tolerance to factor VIII in severe hemophilia. Thromb Haemost 2003; 89: 475-9

21. Sharathkumar A, Lillicrap D, Blanchette VS et al. Intensive exposure to factor VIII is a risk factor for inhibitor development in mild hemophilia A. J Thromb Haemost 2003; 1: 1228-1236

22. Lusher JM. Natural history of inhibitors in severe haemophilia A and B: incidence and prevalence. In: Rodriguez-Merchan EC, Lee CA, eds. Inhibitors in Patients with Haemophilia. Oxford, England: Black-well Science, Ltd, 2002: 3-8

23. Lusher JM. Inhibitor antibodies to factor VIII and factor IX: management. Semin Thromb Hemost 2000; 26: 179-180

24. Scharrer I, Bray G, Neutzling O. Incidence of inhibitors in hemophilia A patients - a review of recent studies of recombinant and plasma-derived factor VIII concentrates. Hemophilia, 1999; 5: 145-154;

25. Aledort LM, DiMichele DM. Inhibitors occur more frequently in African-American And Latino haemophiliacs. Haemophilia, 1998; 4: 68

26. Schwaab R, Brackmann HH, Meyer C et al. Haemophilia A: mutation type determines risk of inhibitor formation. Thromb Haemost, 1995; 74: 1402-1406

27. Bray GL, Gomperts ED, Courter S et al, and the Recombinate Study Group. A multicenter study of recombinant factor VIII (recombinate): safety, efficacy, and inhibitor risk in previously untreated patients with haemophilia A; Blood, 1994; 83: 2428-2435

28. Santagostino E. Gringeri A. Mannucci PM. State of care for hemophilia in pediatric patients. Paediatric Drugs 2002;4(3):149-57.

29. Mariani G, Ghirardini A, Bellocco R: Immune tolerance in hemophilia. Principal results from the international registry. Thromb Haemost 1994;72:155-158

30. Mariani G, Kroner B, Miller RT et al. Immune tolerance in haemophilia with factor VIII inhibitors: predictor of success. Haematologica 2001;86:1186-1193.

31. Mariani G, Siragusa S, Kroner BL. Immune tolerance induction in hemophilia A: A review. Semin Thromb Hemost 2003; 29: 69-76

32. Freiburghaus C, Berntorp E, Ekman M, Gunnarsson J, Kjellberg BM, Nilssom IM. Immunoadsorption for removal of inhibitors: update on treatments in Malmo-Lund between 1980 and 1995. Haemophilia 1998; 4: 16-20

33. Warrier I. Immune tolerance induction in hemophilia B. International immune tolerance registry. Haematologica, 2003; 88: 69-70;

34. Hilgartner M, Knatterud GL and the FEIBA study group. The use of Factor Eight By-passing Activity (FEIBA Immuno) product for treatment of bleeding episodes in haemophiliacs with inhibitor. Blood 1983;61:36-40.

35. Sjamsoedin LJM, Heijnen L, Mauser-Bunschoten EP, Van Geijlswijk JL, Van Houwelingen H, Van Hasten P, Sixma JJ, The effect of activated prothrombin-complex concentrate (FEIBA) on joint and muscle bleeding in patients with hemophilia A and antibodies to factor VIII. New Engl J Med 1981;305:717-21.

36. Nicolaisen EM, Hansen LL, Poulsen F, Glazer S, Hedner U. Immunological aspects of recombinant factor VIIa (rFVIIa) in clinical use. Thromb Haemost 1996;76:200-204.

37. Nicolaisen EM. Antigenicity of activated recombinant factor VII followed through nine years of clinical experience. Blood Coag Fibrinol 1998;9(Suppl 1):S119-S123.

38. Hedner U, Schulman S, Alberts KA et al. Successful use of rFVIIa in a patient with severe haemophilia A subjected to synovectomy. Lancet 1988:1913.

39. Quintana-Molina M, Martínez-Bahamonde F, González-García E, Romero-Garrido J, Villar Camacho A, Jiménez-Yuste V, et al. Surgery in haemophilic patients with inhibitor: 20 years of experience. *Haemophilia* 2004; 10 (suppl 2): 30- 40.

40. Tjønnfjord GE, Brinch L, Gedde-Dahl T, Brosstad FR. Activated prothrombin complex concentrate (FEIBA) treatment during surgery in patients with inhibitors to FVIII/IX. *Haemophilia* 2004, 10: 174- 8.

41. O'Connell N, McMahon C, Smith J, Khair K, Hann I, Liesner R, et al. Recombinant factor VIIa in the management of surgery and acute bleeding episodes in children with haemophilia and high responding inhibitors. *Br J Haematol* 2002, 116: 632- 5.

42. Ingerslev J. Efficacy and safety of recombinant factor VIIa in the prophylaxis of bleeding in various surgical procedures in hemophilic patients with factor VIII and factor IX inhibitors. *Semin Thromb Hemost* 2000; 26: 425- 32.

43. Leissinger CA. Use of prothrombin complex concentrates and activated prothrombin complex concentrates as prophylactic therapy in haemophilia patients with inhibitors. *Haemophilia* 1999; 5 (suppl 3): 25- 32.

44. Shapiro A, Gilchrist GS, Hoots WK, Cooper HA, Gastineau DA. Prospective, randomised trial of two doses of rFVIIa (NovoSeven) in haemophilia patients with inhibitors undergoing surgery. *Thromb Haemost* 198; 80: 773- 8.

45. Lusher J, Ingerslev J, Roberts H, Hedner U. Clinical experience with recombinant factor VIIa. *Blood Coagul Fibrinolysis* 1998; 9: 119- 28.

46. Negrier C, Goudemand J, Sultan Y, Bertrand M, Rothschild C, Lauroua P. Multicenter retrospective study on the utilization of FEIBA in France in patients with factor VIII and factor IX inhibitors. French FEIBA Study Group. Factor Eight Inhibitor Bypassing Activity. *Thromb Haemost* 1997; 77: 1113- 9.

47. Hutchinson RJ, Penner JA, Hensinger RN. Anti-inhibitor coagulant complex (Autoplex) in hemophilia inhibitor patients undergoing synovectomy. *Pediatrics* 1983; 71: 631- 3.

48. Honda K, Nagao T, Kamiya T et al. Prospective matched case control study concerning the treatment and quality of life of hemophiliacs with inhibitors. Rinsho Ketsueki (Japanese Journal of Clinical Hematology) 1998;39:416-21.

49. Gringeri A, Mantovani LG, Scalone L, Mannucci PM. Cost of care and quality of life for patients with haemophilia complicated by inhibitors: the COCIS Study Group. Blood 2003; 102: 2358– 63.

50. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;33(5):337-343.

51. Ware JE Jr, Sherbourne CD. The MOS 36-item Short-Form Health Survey (SF-36). I.Conceptual framework and item selection. Med Care 1992; 30: 473–83.

52. Apolone G, Mosconi P, Ware JE Jr. Questionario sullo Stato di Salute SF-36. Manuale d'uso e guida all'interpretazione dei risultati. Milano, Italy: Guerini e Associati, 1997.

53. Scalone L, Mantovani LG, Mannucci PM, Gringeri A; The COCIS Study Investigators: Quality of life is associated to the orthopaedic status in haemophilic patients with inhibitors. Haemophilia 12:154-162, 2006

54. Morfini M, Haya S, Tagariello G, Pollmann H, Quintana M, Siegmund B, et al: European study on orthopaedic status of haemophilia patients with inhibitors. Haemophilia 13:606-612, 2007

55. Manno CS. Treatment options for bleeding episodes in patients undergoing immune tolerance therapy. Haemophilia 1999;5:33-41.

56. Kulkarni R, Aledort LM, Berntorp E, Brackman HH, Brown D, Cohen AR, Ewing NP, Gringeri A, Gruppo R, Hoots K, Leissenger C, Peerlinck K, Poon MC, Wong WY. Therapeutic choices for patients with hemophilia and high-titer inhibitors. Am J Hematol 2001;67(4):240-6.

57. Scalone L, Gringeri A, Mannucci PM,Von Mackensen S, Mantovani LG: Costs and quality of life in hemophilia: comparison between patients with and patients without inhibitors. Value Health 8:A5, 2005 (abstr)

58. Morfini M, Auerswald G, Kobelt RA, Rivolta GF, Rodriguez-Martorell J, Scaraggi FA, et al: Prophylactic treatment of haemophilia patients with inhibitors: clinical experience with recombinant factor VIIa in European Haemophilia Centres. Haemophilia 13:502-507, 2007

59. Valentino LA: FEIBA prophylaxis for patients with haemophilia and inhibitors. Haemophilia 12:26-31, 2006 (suppl 5)

60. Stephens JM, Joshi AV, Sumner M, Botteman MF: Health economic review of recombinant activated factor VII for treatment of bleeding episodes in hemophilia patients with inhibitors. Expert Opin Pharmacother 8:1127-1136, 2007

61. Solimeno LP, Perfetto OS, Pasta G, Santagostino E: Total joint replacement in patients with inhibitors. Haemophilia 12:113-116, 2006 (suppl 3)

62. Allen G, Aledort L: Therapeutic decision-making in inhibitor patients. Am J Hematol 81:71-72, 2006

63. Astermark J, Morado M, Rocino A, van den Berg HM, von Depka M, Gringeri A, et al: Current European practice in immune tolerance induction therapy in patients with haemophilia and inhibitors. Haemophilia 12:363-371, 2006

64. Monahan PE, Aledort LM; Hemophilia Inhibitor Study Group: Factors affecting choice of hemostatic agent for the hemophilia patient with an inhibitor antibody. Am J Hematol 77:346-350, 2004

65. Astermark J, Rocino A, Von Depka M, Van Den Berg HM, Gringeri A, Mantovani LG, et al: Current use of by-passing agents in Europe in the management of acute bleeds in patients with haemophilia and inhibitors. Haemophilia 13:38-45, 2007

66. Allen G, Aledort L. Therapeutic Decision-Making in Inhibitors Patients. *Am J Hematol* 2006; 81: 71- 2.

67. Ben-Akiva M, Boccara, B. Discrete Choice models with latent choice sets. *International Journal of Research in Marketing* 1995; 12: 9- 24.

68. Adamowicz W, Louviere J, Williams M. Combining revealed and stated preference methods for valuing environmental amenities. *Journal of Environmental Economics,and Management* 1994; 26: 271- 92.

69. Ben-Akiva M & Lerman S. Discrete Choice Analysis: Theory and Application to Travel Demand, 2 edn, *The MIT Press 1985,* Cambridge, Massachusetts.

70. Hensher D. Stated preference analysis of travel choices: the state of practice. *Transportation* 1994; 21: 107- 33.

71. Madden G, Simpson M. Residential broadband subscription demand: an econometric analysis of Australian choice experiment data. *Applied Economics* 1997; 29: 1073- 8.

72. Ryan M, Gerard K. Using discrete choice experiments to value health care programmes: current practice and future research reflections. *Applied Health Economics and Health Policy* 2003; 2 (1): 55- 64.

73. Ryan M, Netten A, Skatum D, Smith P. Using discrete choice experiments to estimate a preference based measure of outcome. An application to social care for older people. *Health Econ* 2006; 25 (5): 927- 44.

74. Mantovani LG, Monzini Ms, Mannucci PM, Scalone L, Villa M, Gringeri A. Differences between patients, physicians and pharmacists preferences for treatment products in haemophilia: a discrete choice experiment. *Haemophilia* (2005); 11: 589– 97

75. Scalone L. Il Disegno dell'Esperimento a Scelte Discrete per la Valutazione delle Preferenze in Sanità. Tesi di Specializzazione in Statistica Sanitaria, conseguita a novembre 2005, presso la Scuola di Specializzazione in Statistica Sanitaria, Facoltà di Medicina e Chirurgia, Università degli Studi di Milano

76. Severin VC, Burgess L, Louviere JJ, Street DJ. Comparing statistical efficiency and respondent efficiency in choice experiments, 2005. Summary of the unpublished PhD Thesis by Severin V (2000), Faculty of Economics and Business, University of Sidney, Australia.

77. Scalone L, Gringeri A, Borghetti F, Ravera S, Casati A, Mantovani LG. Pilot study to establish preferences toward coagulation factor concentrates used to treat people with hemophilia and inhibitors. Poster presented in World Federation Haemophilia Congress, Vancouver, May 21-25 2006.

78. Organization for Economic Co-operation and Development, available at URL www.oecd.org, visited in November 2005.

79. Compendio del servizio sanitario, October 2005; available at URL http://www.ministerosalute.it/

80. World Economic and Financial Surveys – World Economic Outlook Database, April 2005, available at URL www.imf.org.

81. Hahn GJ and Shapiro SS. A Catalogue and Computer Program for the Design and Analysis of Orthogonal Symmetric and Asymmetric Fractional Factorial Experiments. Report 66-C-165, May 1966, general Electric Research and Development Centre, Schenectady, New York.

82. Dawes R, Corrigan B. Linear models in decision making. *Psychol Bull* 1974; 81: 95- 106.

83. Louviere JJ. Why Stated Preference Discrete Choice Modelling is NOT conjoint analysis. *Memetrics White Paper* 2000: 1- 11

84. Carlsson P, Martinsson P. Design techniques for stated preference methods in health economics. *Health Econ* 2003; 12: 281- 94.

85. World Medical Association (WMA) Declaration of Helsinki. Adopted by the 18th WMA General Assembly, held in Helsinki in June 1964.

86. Lancaster KJ. A new approach to consumer theory. Journal of Political Economy, 1966; 74 (2): 132-157

87. McFadden D. Conditional logit analysis of qualitative choice behaviour, in P Zarembka (ed), Frontiers of Econometrics, New York, US, *Academic Press* 1973: 105- 42.

88. Manski CF. The structure of random utility models. *Theory Decis* 1977; 8: 229- 54.

89. Hanemann W. Welfare evaluations in contingent valuation experiments with discrete responses: reply. *American Journal of Agricultural Economics* 1984; 69: 332- 41.

90. Triemstra M, Rosendaal FR, Smit C, Van der Ploeg HM, Briët E: Mortality in patients with hemophilia. Changes in a Dutch population from 1986 to 1992 and 1973 to 1986. Ann Intern Med 123:823-827, 1995

91. Lee WC, Joshi AV, Woolford S, Sumner M, Brown M, Hadker N, Pashos CL. Physicians' preferences towards coagulation factor concentrates in the treatment of Haemophilia with inhibitors: a discrete choice experiment. *Haemophilia* 2008; Volume 14 (3): 454- 65(12).

92. Ratcliffe J. The use of conjoint analysis to elicit willingness-to-pay values. Proceed with caution? Int J Technol Assess Health Care 2000; 16 (1): 270– 5.

93. Samuelson PA, Nordhaus WD: Economics. Columbus, OH, McGraw-Hill, 2004