

**A Novel Analysis of Hemophilia Treatment Administration on Patient Utility: Combining a
Discrete Choice Experiment (DCE) with Time Trade-Off (TTO) Estimation-DCE_{TTO}**

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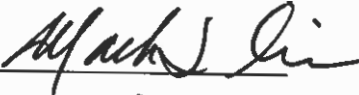
Dissertation

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ABSTRACT

A Novel Analysis of Hemophilia Treatment Administration on Patient Utility: Combining a Discrete Choice Experiment (DCE) with Time Trade-Off (TTO) Estimation-DCE_{TTO}

Objectives: Hemophilia A treatments differ in the method and frequency of administration. This study aims to elicit preferences of patients with hemophilia A (PWH) and quantify the incremental impact of treatment attribute changes on health utility by utilizing a discrete choice experiment (DCE) and a DCE with time trade-off (TTO) DCE_{TTO} methodology.

Methods: An analysis was performed of 115 PWH (mean age 37 years, range 18-70) recruited from the Louisiana Center for Bleeding and Clotting Disorders at Tulane's Hemophilia Treatment Center, and the National Hemophilia Foundation who participated in a web-based or in-clinic survey. Treatment attributes were based on the core outcome set for hemophilia gene therapy (coreHEM) and included method and frequency of administration, mental health, chronic pain, and annual bleeding rate. For the DCE_{TTO}, 10-, 15-, and 20-year durations were used. Patients completed 12 DCE and 12 DCE_{TTO} tasks. Choices were analyzed using conditional logistic models. And socio-demographic data, clinical characteristics and EQ-5D-5L were obtained from medical records or were self-reported.

Results: Approximately 57% of PWH reported moderately burdensome treatment (22% treat > once/week). The mean EQ-5D-5L Visual Analog Scale (VAS) was 75 and mean EQ-5D-5L utility score was 0.684. In the DCE all attributes were statistically significant, with administration being the most important attribute (2-3 times IV infusion per week vs. 10-year durability utility of -1.99), mental health (always concerned vs. no concern utility of -1.37), bleeding (5 or more vs. none utility of -0.73), and finally chronic pain (yes vs. no utility of -

0.36). In the DCE_{TTO}, treatment with multiple IV infusions weekly was associated with an annualized utility decrement (0.046 vs. 10-year durability, 0.044 vs. 5-year). And treatment with multiple SQ injections monthly was associated with an annualized utility decrement (0.037 vs. 10-year durability, 0.030 vs. 5-year).

Conclusion: All coreHEM outcomes are important for treatment choices of PWHA. A one-time IV treatment can provide important utility for PWHA over currently available treatments.

INTRODUCTION

Hemophilia A is a sex-linked inherited bleeding disorders due respectively to the deficiency of coagulation factor VIII (8). Approximately 70% of patients with hemophilia are inherited, while the other 30% are caused by spontaneous FVIII gene mutations. Overall, hemophilia affects 1 in 5000 live male births in United States, and 1 in 10,000 male births worldwide, among which hemophilia A patients make about 80%. There are approximately 20,000-33,000 hemophilia patients currently in the United States. Hemophilia affects people from all racial and ethnic groups (CDC, 2020).

Hemophilia A is a recessive bleeding disorder that is most commonly caused by a FVIII gene mutation within the Xq28 region of the X chromosome. Patients with hemophilia A have a deficiency or absence of blood coagulation factor VIII (FVIII), an essential component of the intrinsic pathway in the coagulation cascade (Mannucci and Tuddenham 2001; Franchini and Mannucci 2013). This leads to frequent bleeding events, including easy bruising, prolonged bleeding after trauma, intracranial hemorrhage, and spontaneous bleeding into joint, muscles, or soft tissues. The hallmark of hemophilia is joint bleeding, most frequently affecting the knees, elbows, and ankles. When a patient experiences repeated bleeding in the same joint, this is called a target joint; hemophilic arthropathy, which results in progressive degeneration of the joint cartilage and bone (Srivastava et al., 2020). Patients with hemophilia are not only affected by the lifelong bleeding tendency, but also suffer from local functional deficits, hemorrhagic shock, neurocognitive defects, or even death.

Thus, patients with mild hemophilia A tend to experience abnormal bleeding only in response to surgery, tooth extraction, or injuries. Conversely, patients with moderate hemophilia A experience prolonged bleeding responses to relatively minor trauma, and patients with severe

hemophilia A experience frequent spontaneous bleeds, especially recurrent hemarthroses and soft-tissue hematomas. Over time this leads to severe arthropathy, joint contractures, and pseudo tumors and, consequently, to chronic pain, disability, and a reduced quality of life (Franchini et al. 2013).

Resource Dependence Theory-Hemophilia Treatment Center

Good quality medical care from doctors and nurses who are knowledgeable about hemophilia can help prevent some serious problems. Often, the best choice for care is to visit a comprehensive hemophilia treatment center. According to Community Counts (2018), a public health monitoring program funded by CDC's Division of Blood Disorders, there are currently 141 hemophilia treatment centers located throughout the United States. Within these hemophilia treatment centers, not including those patients who are not seen at hemophilia treatment centers, there are 17,979 patients with FVIII deficiency and 5,717 persons with FIX deficiency, who were reported from 1/1/2012 through 03/31/2018 (CDC, 2018). A hemophilia treatment center not only provides care to address all issues related to the disorder, but also provides health education that helps people with hemophilia stay healthy.

Resource dependence theory explains the relationship between the external environment and how it influences the strategy, structure, and performance of the hemophilia treatment center. The resource dependence model proceeds from the indisputable proposition that organizations are not able to internally generate either all the resources or functions required to maintain themselves, and therefore organizations must enter into transactions and relations with elements in the environment that can supply the required resources and services (Aldrich & Pfeffer, 1976). Specifically, resource dependence theory posits that each organization is an open system and, typically, individual organizations do not control all the necessary resources needed for

organizational survival and development. Therefore, every organization depends, to some extent, on the external environment to satisfy their resource needs (Yeager, Yongkang, & Diana, 2015).

The resource dependence model portrays the organization as active, and capable of changing, as well as responding to, the environment. Since the environment, according to the resource dependence perspective, does not impose as strict requirements for survival, many possible actions and structures are consistent with the survival of the organization (Aldrich & Pfeffer, 1976). According to Alexander and Morrissey (1989), organizational survival is dependent on the acquisition of necessary resources from the environment. In the case of hemophilia treatment centers, these resources include patients, physicians, capital, favorable regulation, in addition to several other resources to run the center.

Running and maintaining an organization means mobilizing several kinds of scarce resources. Organization builders must accumulate capital, commitment of potential members, entrepreneurial skills, and legitimacy. Organizations continually use substantial portions of their resources in maintaining and reproducing their structures (Hannan & Freeman, 1984). The same applies to the resources needed for a hemophilia treatment center.

Over thirty years ago, parents faced with the crippling and possible death of their hemophilic children formed a bond with their physicians that led to the development of an extremely effective health advocacy collaboration. That partnership created a nationwide hemophilia health delivery system that has grown beyond medical care to include research and the public health functions of needs assessment, capacity building, surveillance, prevention, and policy (Resnick, 1999). In 1975, section 1131 of the Public Health Service Act established and funded a network of Hemophilia Diagnostic and Treatment Centers throughout the United States (Smith, Levine, & Directors, 1984). The functions of hemophilia treatment centers, according to

the World Federation of Hemophilia (2012), are to provide and coordinate inpatient and outpatient care, and services to patients and their families.

The core hemophilia treatment center team is comprised of experts from four disciplines: a board-certified hematologist who serves as hemophilia treatment center director, a nurse coordinator, a social worker, and a physical therapist. This team consults with subspecialists including those in dentistry, genetics, orthopedics, infectious disease, hepatology, and pharmacy (Baker, Crudder, Riske, Bias, & Forsberg, 2005). This core team of individuals and subspecialists, in the hemophilia treatment center, are considered external factors.

The clinicians and staff of the hemophilia treatment center, provide care and services to patients and families. Patients need follow up and should be seen by all core team members at least once a year, if not every six months, depending on the patient's severity of disease. The follow up visits should involve complete hematologic, musculoskeletal, and psychological assessments. And during each follow up visit, the patient's comprehensive management plan should constantly be refined. If a patient needs a referral, this should also happen during this visit. Due to the complexity and sometimes uncertainty of when a patient may or may not get a bleed, the patient and/or patient's family must know how to administer factor. Hemophilia treatment centers initiate, and provide training to patients and their families, on how to administer home therapy with clotting factor.

The environment of the hemophilia treatment center also plays a role for patient access. Hemophilia treatment centers are typically housed in university-based tertiary care hospitals, offering a full range of outpatient and inpatient services including case management and collaboration with primary care practitioners and other subspecialists (Baker et al., 2005). Universities with tertiary based hospitals are usually located in cities, places that are easily

accessible and centrally located. The time in which this becomes an issue, is if the patient lives outside of the city. Many of the larger HTC's increase individuals' access to hemophilia care by operating satellite clinics in rural areas and by offering telephone counseling to patients in remote or underserved areas (Zhou et al., 2011). In this case, a few hemophilia treatment centers, such as the Louisiana Center for Bleeding and Clotting Disorders, have clinics once a month and quarterly in rural locations, for those patients who cannot make it to main hemophilia treatment center location.

The hemophilia treatment center environment should also have access to the following resources: A coagulation laboratory capable of performing accurate and precise clotting factor assays and inhibitor testing. A supply of appropriate clotting factor concentrates, either plasma-derived or recombinant, as well as other adjunct hemostatic agents such as desmopressin (DDAVP) and tranexamic acid where possible. Where clotting factor concentrates are not available, access to safe blood components such as fresh frozen plasma (FFP) and cryoprecipitate. And access to casting and/or splinting for immobilization and mobility/support aids, as needed (WHF, 2012).

Hemophilia treatment centers should ensure that people with hemophilia have access to the full range of services necessary to manage their hemophilia. The keys to improving health and quality of life in people with hemophilia include prevention of bleeding, long-term management of joint and muscle damage, and management of complications from treatment including inhibitor development and transfusion-transmitted infections (Colvin et al., 2008).

Munificence-Hemophilia Treatment Center

Munificence refers to the availability and accessibility of resources necessary for an organization's survival and development within its external environment. A munificent

environment is important because it can provide financial, professional, and other resources needed but not possessed by organizations (Yeager, Yongkang, & Diana, 2015). Because resources can range from being abundant or scarce and can change over time, the resource dependence theory perspective predicts that successful organizations must develop strategies that take advantage of munificence in their environment (Yeager, Menachemi, Savage, Ginter Sen, & Beitsch, (2014). It is assumed that patients receiving hemophilia treatment in a munificent environment, specifically hemophilia treatment centers, are more likely to have better patient outcomes, compared to those who do not receive treatment in a munificent environment. These outcomes include fewer bleeds, fewer hospital visits, fewer deaths, access to factor clotting products, and better management of their hemophilia when it pertains to quality of life.

An important resource to the hemophilia treatment center involves funding, which is used to pay staff, and provide services to patients and families. Munificence comes into play specifically, when it comes to funding, or rather the finances of the hemophilia treatment center. This funding can come from government agencies such as the CDC, HRSA, and/or from private donors.

In 1992 Congress established the 340B Drug Pricing Program (340B program), as part of the Public Health Service Act which allows designated covered entities. The covered entity in this paper is, a comprehensive hemophilia diagnostic treatment center receiving a grant under section 501(a)(2) of the Social Security Act (PSA, 2018), to purchase pharmaceutical products at a discounted rate. Through this program, hemophilia treatment centers can establish a pharmacy to purchase and sell clotting factor and other drugs, used by their patients to treat their bleeding disorders (HRSA, 2017). Hemophilia treatment centers can thereby, augment scarce federal resources and generate program income. The program income generated by the

sale of the products, by law, must be used for patient health, education, and supportive services necessary to provide comprehensive care to patients served by the hemophilia treatment centers.

Hemophilia treatment centers are eligible as covered entities to use pharmacy income from the 340B program to support clinical staff and patient services. Much of this program income is used to support personnel (Malouin et al., 2018). With adequate financial resources, it is assumed that hemophilia treatment centers with greater financial resources from the 340B program, have better patient outcomes than those hemophilia treatment centers who do not have resources from the 340B program.

In 2014, the National Hemophilia Program Coordinating Center (NHPCC), conducted the first national survey at 83 hemophilia treatment centers, to assess the impact of the 340B program income on the hemophilia treatment center's capacity to deliver and sustain services. The survey collected data to demonstrate the value of the 340B program in supporting and enhancing services offered by the hemophilia treatment centers. Findings showed that more than 90 percent of the social work, nursing, and vocational services of hemophilia treatment centers are funded through 340B program income, as well as the majority of costs associated with outreach programs, telemedicine, home visits, and care coordination.

Even beyond providing health care assessment at hemophilia treatment centers, core staff spend an extensive amount of time on telephone triage and medical coordination. This ongoing integrated care management is critical to prevent complications that can lead to progressive joint disease, disability, and loss of income for the affected individual. As well as increased medical and social costs to society (Malouin, 2018). All of this is made possible with funds from the 340B program.

In addition, access to specialized care is challenging for patient who live far from a hemophilia treatment center. Three of the most frequently cited barriers for patients in seeking treatment at a hemophilia treatment center were distance to the center, clinic hours were not convenient, and transportation to the center (Saxena, 2013). The core staff must coordinate care with local providers, closer to where the patient lives, and other specialists who lack knowledge on treating hemophilia, in order to educate and train them. All of this is made possible with funds from the 340B program.

The individual costs of a patient with hemophilia varies on the severity of disease, complications, and treatment regimen, and patients experience financial barriers related to the cost of clotting factor products. Majority of these costs include clotting factor medication, clinic visits, hospitalization, medical and surgical procedures, and laboratory tests. Published estimates suggest that mean healthcare costs for patients with hemophilia in the United States reach upward of \$140,000 per year in the absence of inhibitors. Based on 2010 Medicare spending, treatments for hemophilia are the costliest drug average per beneficiary (Guh, Grosse, McAlister, Kessler, & Soucie, 2012). Lifelong treatment with factor-replacement therapy, either as prophylaxis or as acute or on-demand therapy, is the mainstay of hemophilia management. Spending on factor replacement therapy makes up over 80% of the total direct expenditures for patients with hemophilia (Chen, 2016).

Clotting factor purchased through the 340B program is for outpatient use only, and in certain instances, hemophilia treatment centers can provide factor to patients who participate in the 340B program. The 340B program allows hemophilia treatment centers to purchase clotting factor at a discount for their patients. By treating bleeding quickly, painful and costly complications, resulting in emergency treatment, can be avoided. The average annual cost of

treating individuals affected with mild hemophilia, without complications, is approximately \$59,101 per patient and \$301,392 for patients with severe hemophilia receiving prophylactic treatment (Zhou et al. 2015). Home therapy facilitates early treatment of bleeding episodes, but it requires intensive patient training and close monitoring by the health care professional (Soucie et al., 2000). Along with providing training to patients, hemophilia treatment centers educate patients, family members and other caregivers to ensure that the needs of the person with hemophilia are met.

The way that a hemophilia treatment center is organized, is to provide each patient with access to multiple medical disciplines, each of which has specific experience in hemophilia care. This integration of services maximizes both the effectiveness and the efficiency of the health care program. Over 21,000 persons with hemophilia are treated in the HTC network, representing approximately 67% of the 31,000 affected by hemophilia in the United States (Malouin et al., 2018). It is estimated that 30% of persons with hemophilia in the United States do not receive care at federally funded hemophilia treatment centers. These estimates suggest that perhaps 6,000 individuals with hemophilia and an unknown number of persons with other genetic bleeding disorders receive care elsewhere (Owens, Oakley, Le, & Byams, 2016).

In 1984, an article was published by Smith & Levine, which collected outcome data of 11 hemophilia treatment centers, before and after five years of implementing a comprehensive hemophilia treatment center. Improved health, decreased hospitalization, decreased absenteeism, and a decrease in the unemployment rate from 36 percent to 13 percent were accompanied by decreased costs of care, after implementing the comprehensive hemophilia treatment center. This was just the beginning of the hemophilia treatment center, and as resources have increased, patient outcomes have continued to improve.

Butler et al., in 2016 published an article which conducted a national needs assessment of hemophilia treatment center patients in the United States. It was one of the largest assessments of the hemophilia treatment center population. Ninety-eight percent of patients reported that care at a hemophilia treatment center is important to them, with 2% stating that care at a hemophilia treatment center was not important. Overall, the survey indicated that patients received the services they needed, and these services met their needs.

Hemophilia treatment centers, health service utilization grew between 2002 and 2010, by increases in diagnostic evaluations, annual comprehensive examinations, and home intravenous therapy (Baker et al., 2013). It is clear that hemophilia treatment centers with adequate resources have improved patient outcomes. It has been demonstrated that the benefits of establishing hemophilia centers are observed even in developing countries and that changes can be achieved when resources are reorganized, especially when education and training are provided at all levels (Ruiz-Saez, A., 2012).

To manage hemophilia, requires comprehensive health services. 340B program funds are a driver behind several components of the hemophilia treatment center. The 340B program not only provides factor to patients at a discounted rate, but also funds the positions of several hemophilia treatment center core team members, such as the social worker, physical therapist, nurse, etc. All of these aspects are needed in order to manage the disease and improve patient outcomes.

Patients treated as part of a hemophilia treatment center, experience better outcomes than patients cared for outside of the hemophilia treatment center network, even though the population treated within a hemophilia treatment center, is composed of a higher percentage of patients with severe disease and those with blood-borne viral infections and/or inhibitors. Also,

patients treated within the hemophilia treatment center network experienced a significant reduction in bleeding-related hospitalizations, especially those on home therapy, compared with patients without an HTC relationship (Soucie, 2000). This proves that patients who receive hemophilia treatment care in a munificent environment, meaning a hemophilia treatment center, have better outcomes. These environments thrive off of 340B program funding, which in turn can provide the resources needed to fund the hemophilia treatment center, for better outcomes.

While data shows that patients treated at hemophilia treatment centers have better outcomes, information on patients who do not receive their care at a hemophilia treatment center is limited. One of the reasons, is that identifying the patients is more difficult. Another reason is that the care they receive most likely comes from a primary care physician or specialist, whose main focus is not hemophilia. More research is needed to get this information, considering health care facilities that do not have a hemophilia treatment center, and/or those health care centers not a part of a tertiary care hospitals.

Due to so much emphasis, placed on hemophilia treatment centers who receive 340B program funding, there is lesser data found on centers who do not receive 340B funding. It would almost make sense, that every hemophilia treatment center would also be a part of the 340B program, but that does not hold true. It also requires a good amount of work on the administrative side of the hemophilia treatment center, to keep up the requirements of the 340B program. Meaning, some centers can lose their 340B program funding, if not compliant. Once again, more research is needed, in order to find out why hemophilia treatment centers do not participate in the 340B program, in addition to collecting data on patient outcomes.

Through comprehensive support, in addition to 340B program funding, hemophilia can be treated and managed successfully. The goal is to decrease morbidity and mortality, avoid

unnecessary trips to the emergency department, and wasting of expensive clotting factor. By providing and having access to resources within a hemophilia treatment center, these goals can be obtained.

Treatment

The best way to treat hemophilia is to replace the missing blood clotting factor so that the blood can clot properly. Treatment of severe hemophilia A presently consists of intravenous injection (administering through a vein) of plasma-derived or recombinant human FVIII. Clinicians typically prescribe treatment products for episodic care or prophylactic care. Episodic care, also called on-demand is used to stop a patients' bleeding episodes, at the time of a bleed, to prevent or control bleeding episodes, respectively. Prophylactic care, usually 2-3 times per week is used to prevent bleeding episodes from occurring. Today, people with hemophilia and their families can learn how to give their own clotting factor treatment products at home.

The half-life for FVIII (12 to 18 hours for most approved products), necessitates frequent infusions, and although major advances in the treatment, it remains common for severe patients to continue to have multiple bleeding events on prophylactic and on-demand-only therapy. The consequence of multiple bleeding events is the development of debilitating multiple-joint arthropathy and substantially increased risk of death. There is, therefore, a strong unmet need for a fully preventive treatment of hemophilia A to give patients a factor level compatible with a normal and hemorrhage-free life. There is an unmet need for a novel technology that may remove the burden of frequent repeated injections. Recently, the FDA (2018) approved the non-factor treatment of emicizumab which is given subcutaneously weekly, every two weeks, or every four weeks in hemophilia A patients with and without inhibitors. And even more recently,

Altuviiiio was FDA (2023) approved which is a high-sustained factor VIII replacement therapy that is administered intravenously once weekly.

The frequency of treatment in both emicizumab and altuviiiio is less than regular FVIII treatments. Emicizumab bridges both factor IXa and factor X to restore the function of missing activated factor VIII in patients with hemophilia A. It has a long plasma half-life and high subcutaneous bioavailability. So, it is not required for repeated infusions without venous access (Lingamaiah et al., 2022). Globally, the introduction of emicizumab has facilitated the acceptance of prophylaxis as the new global standard of care in inhibitor and non-inhibitor hemophilia A patient management (Mahlangu, Iorio, & Kenet, 2022).

Altuviiiio combines Fc Fusion, which helps FVIII recirculate in the blood, XTEN Technology, which shields FVIII from breaking down too early, and vWF fragments to keep FVIII in the blood longer (Bioverativ, 2023). It is a new type of FVIII replacement with an extended half-life allowing once weekly dosing to achieve hemostasis. This provides a highly effective option for treatment and prevention of bleeding in patients with hemophilia A and provides an option for treatment of bleeding and coverage for surgery with few infusions (Konkle, 2023). It delivers normal to near-normal factor activity levels for most of the week with once-weekly dosing, and significantly reduces bleeds compared to prior factor VIII prophylaxis (ASH, 2023).

Gene therapy offers the potential of disease-modifying therapy by continuous endogenous production of active FVIII following the single intravenous infusion of a vector encoding the appropriate gene sequence via long-term episomal expression. Hemophilia A is well-suited for a gene replacement appropriate gene sequence for long-term episomal expression because clinical manifestations are attributable to the lack of a single gene product (FVIII) that circulates in minute

amounts in the plasma. Tightly regulated control of gene expression is not essential, and even modest increases in the level of FVIII (any increase of the plasma level by 2 ng/ml induces an increase in activity of 1%) can ameliorate the severe form of hemophilia A. Thus, relatively small changes in endogenous FVIII activity can result in clinically relevant improvements in disease phenotype. Finally, the circulating FVIII response to gene transduction can be assessed using validated quantitative rather than qualitative endpoints that are easily assayed using established laboratory techniques (BioMarin 2017).

At least 2 years after the gene transfer, study data showed durability of FVIII activity and bleeding reduction, and the safety profile of valoctocogene roxaparvovec for persons with mild-to-moderate HA (Mahlangu et al., 2023). Three years after gene therapy with AAV5-hFVIII-SQ vector in participants with hemophilia A resulted in sustained, clinically relevant benefit, as measured by a substantial reduction in annualized rates of bleeding events and complete cessation of prophylactic factor VIII use in all participants (Pasi et al., 2020). Valoctocogene roxaparvovec is approved by the European Medicines Agency, and as of June 29th, 2023, has been approved by the Federal Drug Administration (FDA).

coreHEM Framework

In 2018, a core outcome set for gene therapy was developed called coreHEM. The uniqueness of this development was that it involved multiple stakeholders; 49 participants (five patients, five clinicians, five researchers, 12 drug developers, four regulators, nine payers, six health technology assessors, and three research agencies), which was a first. This group of stakeholders wanted to create outcomes measures required to evaluate efficacy, safety, comparative effectiveness, and value of gene therapy for hemophilia (Iorio et al., 2018).

The process used to select the core outcome set was a modified Delphi consensus process. This is when a set of outcomes is presented to the stakeholders, and they are asked to rate their importance on a scale of 1 (not important to include) to 9 (essential to included). Stakeholders could also suggest new outcomes to include. If $\geq 70\%$ of all voters rated an outcome with a score of 7-9, it was selected as part of the coreHEM, or if $< 70\%$ of voters rated 7-9, but the stakeholders in the patient group gave the outcome an average rating of ≥ 7 , it was selected. The outcome set initially started with 48 outcomes, and after three rounds of voting, was narrowed down to six final coreHEM outcomes (Figure 1).

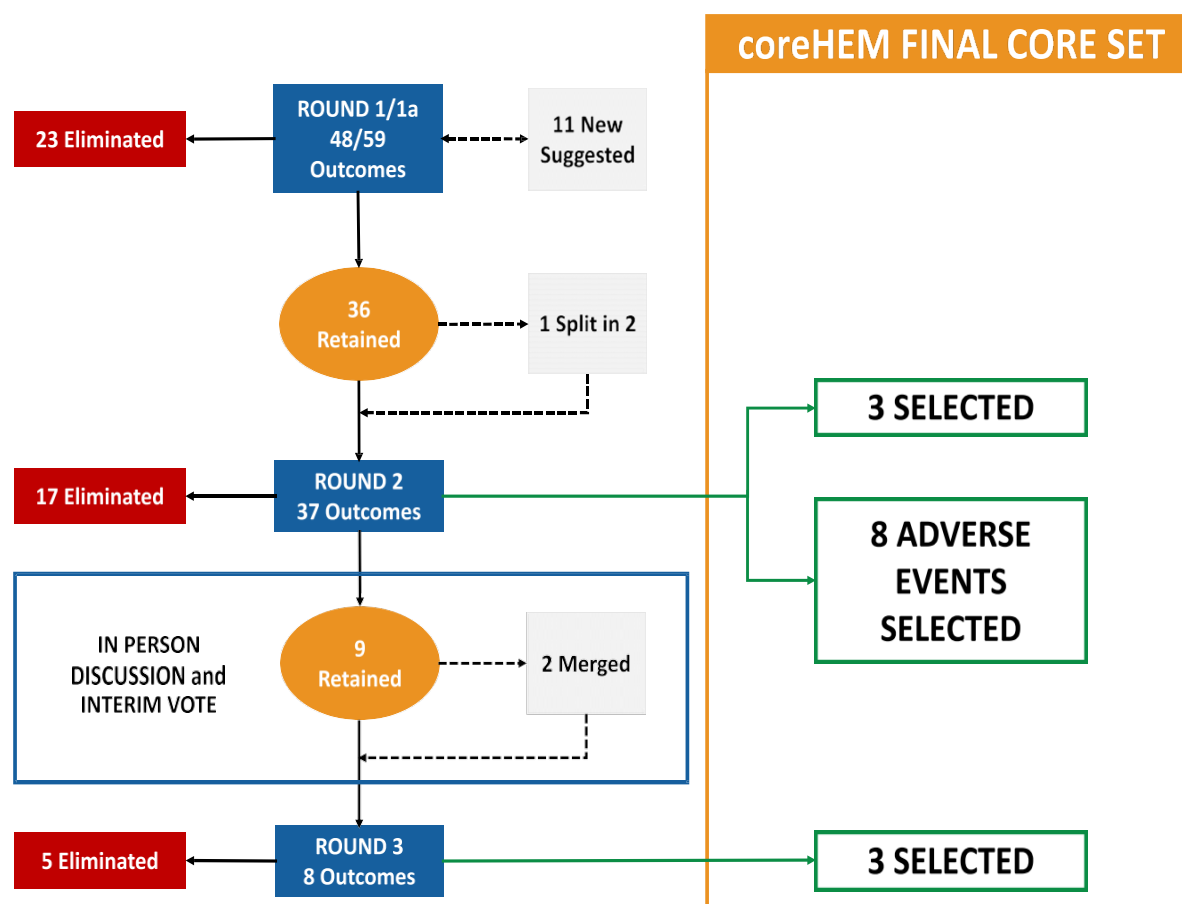


Figure 1: Note this flowchart of coreHEM process was produced by Iorio et al., in 2018. Iorio, A., Skinner, M. W., Clearfield, E., Messner, D., Pierce, G. F., Witkop, M., Tunis, S., & coreHEM panel (2018). Core outcome set for gene therapy in haemophilia: Results of the coreHEM multistakeholder project. *Haemophilia : the official journal of the World Federation of Hemophilia*, 24(4), e167–e172.

The final set of core coreHEM outcomes decided upon was frequency of bleeds, factor activity levels, duration of expression, chronic pain, utilization of health system, and mental health. Frequency bleeds means the annual bleed rate. The factor activity level is measuring the level of factor VIII in the blood. Duration of expression means the amount of time factor VIII levels are maintained after treatment, and in this case, gene therapy. Chronic pain pertains to the duration and intensity of pain. Utilization of health system means the amount it costs to treat a patient's hemophilia, such as health care in general, doctor visits, and factor costs. And mental health, the quality of life of a patient with hemophilia.

coreHEM has also been integrated into the outcomes list for the Institute for Clinical and Economic Review (ICER). ICER is an organization that evaluates medical evidence and then works with stakeholders to interpret and apply evidence to improve patient outcomes and health care costs (ICER, 2022). Based on the coreHEM outcomes, ICER has published the outcomes, which have been disseminated to various hemophilia treatment centers and organizations, in hopes of improved patient care.

The patient perspective in coreHEM is important because patients can have “say” about what is important to them, when it comes to their care and treating their hemophilia. Patients also appreciate when, specifically providers, listen to them, and make them feel valued about how they feel and the treatment that they receive. Therapies such as gene therapy, can change the standard of care, which can change patient expectations and priorities. What is most important to patients may reveal differences between the patients and other stakeholders, which will impact the outcome, but will also inform stakeholders of outcomes that have possibly been overlooked. Prioritizing how patients feel from the start of developing coreHEM empowers the patients. Patients can provide valuable insight to other stakeholder groups which may extend beyond the

development of the core set and into decision-making at each stage of the lifecycle of a product, including those by post-regulatory decision-makers, such as HTA groups, payers, and clinicians (Clearfield, 2023).

Significance of Research

Recombinant FVIII concentrate, emicizumab, altuviiio, and gene therapy differ with respect to method of administration, frequency of administration, site of administration, adverse events, efficacy, ability to induce inhibitors and potentially years to life. In addition, gene therapy is administered once in the patient's lifetime, followed by the return to regular therapies. These differences provide challenges for hemophilia treatment centers, the point of care for clinicians communicating the differences, and for patients in making trade-offs between treatment characteristics. In addition, bleeding and adherence to the treatment regimen continues to be a problem for many patients. This study involves the development of a valid DCE survey instrument, in combination with TTO attribute, to be given to patients with hemophilia A, to elicit health utilities for hemophilia A treatment attributes, particularly for treatment administration modes, thus a DCE_{TTO}.

Objectives

The **primary objective** of this project is to conduct a DCE to elicit preferences of patients with Hemophilia A and to estimate the relative importance of treatment attributes in regard to gene therapy, implementing TTO methodology, to inform treatment decision making (DCE_{TTO}).

The **secondary objective** is to investigate quality of life measures in Hemophilia A patients utilizing the EQ-5D-5L.

METHODS

In a DCE, there must be a balance between what may be important to the patient and what is relevant to the decision-making environment. Evidence to support inclusion or exclusion of certain treatment attributes can be assessed through literature reviews and other evidence of the impact of disease as well as the nature of the treatments being assessed. Clinical expert consultation, qualitative research, or other studies can provide a basis for identifying a set of attributes and levels that appropriately and comprehensively characterize treatment profiles to be compared (Bridges et al., 2011). These criteria are met by involving key design strategies in the development of the instrument, conducting reviews of literature, and conducting pretesting (pilot) with a select group of patients.

The selection of DCE treatment profile attributes and levels that characterize treatments, was informed by the core outcome set for hemophilia gene therapy (coreHEM). As stated in the introduction, CoreHEM outcomes evaluate efficacy, safety, comparative effectiveness, and value of gene therapy for patients with hemophilia. And the outcome measures were developed with the involvement of various stakeholder groups, including patients. Specifically for this project, the attributes chosen for the DCE were method and frequency of administration, mental health, chronic pain, and annual bleeding rate

The TTO method elicits health utilities for health states by letting a patient imagine living a defined number of years in an imperfect health state. The patient then has to indicate the number of remaining life years in full health at which the patient is indifferent between the longer period of impaired health and the shorter period of full health (Attema, Edelaar-Peeters, Versteegh, & Stolk, 2013). Patient preferences for treatment characteristics and the rate at which they are willing to trade-off between certain characteristics can be understood and possibly

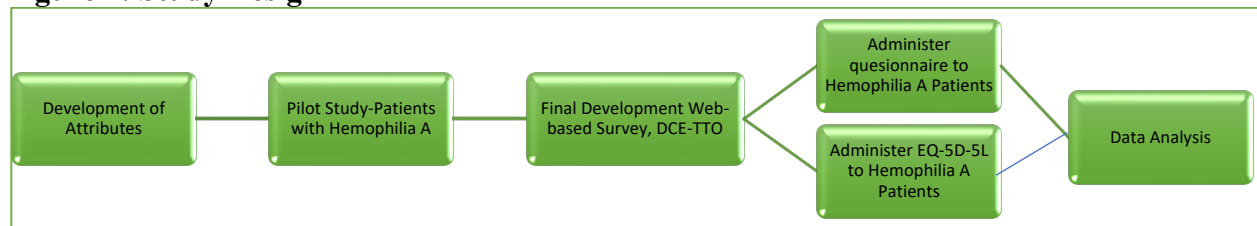
quantified through design and administration of a DCE_{TTO}, a type of conjoint analysis. For the TTO, 10-, 15-, and 20-year durations were used. In a DCE_{TTO}, patients must choose their most preferred treatment alternative from a set of treatment profiles, assuming that these are the only treatment options available. Discrete choice experiments, therefore, allow one to compare the relative importance of various treatment attributes.

Study Design

A DCE_{TTO} survey instrument, was designed and administered, via a web-based platform, to consented patients with hemophilia A, at the Louisiana Center for Bleeding and Clotting Disorders (LCBCD) at Tulane University School of Medicine (New Orleans, LA) and the National Hemophilia Foundation (NHF). Specifically, the study elicits patient preferences for outcomes associated with the treatments of hemophilia A. Each hypothetical treatment alternative was defined by bleed rate, treatment characteristics, mental health, chronic pain, and life duration as TTO attribute. The DCE_{TTO} survey instrument requires constructing a series of 24 choices sets that evaluate hemophilia A. Each hypothetical treatment profile consists of combinations of attribute levels. In general, the survey should be completed within 20-25 minutes. The combination of attributes and levels that patients evaluate in a choice-experiment survey is known as the experimental design. These combinations must have statistical properties that allow estimating the preference weights of interest. And lastly, the EQ-5D-5L, a generic quality of life measure, is a questionnaire that is used to indirectly estimate the utility of a health state. EQ-5D-5L is one of the most commonly used generic health status measurements, and its

validity and reliability have been reported for various health conditions. Patients are asked to rank their current health in five different dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depressions. Answers are chosen from five response levels.

Figure 2: Study Design



Pilot Questionnaire

A pilot study (n=5) was conducted with a small sample of patients with Hemophilia A to examine the physiological burden of each hypothetical treatment alternative (Appendix A). Based on the patient characteristics and demographics, the average age of the patient was 44, with 27 being the youngest and 62 being the oldest. Two patients are Black and three are White. All patients have severe disease, except for one with moderate disease, and none had history of inhibitor, all on prophylactic treatment, and none had a history of central device. Three patients had joint problems in the past year, but none had joint procedures. Two patients have HIV, and three had a history of Hepatitis C. All patients have commercial insurance, except one for with public insurance. Two patients have a college education, one a post graduate education, one some college education, and one an associate degree (RN). Three are married and two are single.

When the patients were asked about bleeds, two patients had 1-2 bleeds, two patients had 3-4 bleeds, and one had no bleeds within the past year. When asked what level of risk they were comfortable with developing a thrombotic clot, four stated low and one stated medium risk; developing liver inflammation, four stated low and one stated medium risk; and long-term safety side effects, three stated low, one stated medium, and one stated high risk.

When patients were asked about mode and frequency of treatment administration, four stated that they preferred a one-time infusion, and one stated no treatment at all. And when asked how often they prefer to receive treatment, three stated once every 10 years, one stated once every 5 years, and one stated 1-2 times a month. All patients would like to be able to perform high level of normal activities without fear of bleeding. Whereas, when asked if they would consider a treatment that would determine the number of years lived, if it meant living fewer years, but their hemophilia A was “cured,” all stated, no.

Patients were also asked their thoughts on the survey, and all except for one felt like the questions were written clearly, relevant, and normal to their hemophilia A treatment. One patient stated that he felt like the questions were not written clearly, a little confusing, strange, and were not relevant to his hemophilia A treatment. All expressed the importance of quality of life, prevention of bleeds, and effectiveness and safety of treatment. In addition, one patient stated that living longer was important. When asked their thoughts on gene therapy, all were interested, but hesitant, because there is not enough data to allow them to decide if they would get gene therapy or not. One patient specifically stated that he was very excited and encouraged about gene therapy, while another stated that he does not want his genes “messed” with, and it may cause more problems.

Based on their responses, and understanding of the questions, an online survey using the DCE_{TTO} methodology focusing on gene therapy, was designed to capture preferences for treatment characteristics for patients with hemophilia A (Appendix B). Treatment-related characteristics, defined based on literature and interviews with patients, included bleed rate, treatment patterns, daily activities, and life duration. The duration of life (10, 15, 20 years), which is the key element for TTO, was included as an attribute to articulate the hypothetical health status scenarios reflected in a rare disease(s). The goal was to create a total of, no more than 4 attributes with varying levels, that define the choice sets (Appendix C)

In addition, participant characteristics and demographics including age, race, sex, education level, employment status, income level, marital status, comorbidities, and self-reported general health status as appropriate, were collected (Appendix D). And the EQ-5D-5L, a quality-of-life assessment (Appendix E) was administered.

Patient Population

Inclusion: Patients who are eligible to be included in the DCE_{TTO} should meet the following criteria:

1. Males \geq 18 years of age with hemophilia A
2. Must have been on prophylactic FVIII replacement therapy for at least 12 months prior to study entry, be on on-demand or non-factor treatment, such as emicizumab.
3. Are able complete the survey instrument
4. Willing and able to provide written, signed informed consent

Exclusion: Patients who meet any of the following criteria are not eligible to participate in the study:

1. Males < 18 years of age, females
2. Patients who are currently not on any treatment

3. Are not able to complete the survey
4. Unable to provide consent

All patients were recruited from the LCBCD at Tulane University School of Medicine, and NHF. Patients were not eligible if they did not meet these criteria.

Sample size

Approximately, 80-100 patients with hemophilia A, were recruited. The sample size was estimated based on the main effects the statistical model by Louviere's sample size estimation method. Sample-size calculations represent a challenge in the choice experiment. (1) The minimum sample size depends on several criteria including the question format, the complexity of the choice task, and the desired precision of the results. (2) Based on the literature, a choice-experiment study design with 4 attributes, each with 2-4 levels, 24 choice sets per patient, and 2 choices in each set (e.g., patient chooses treatment A or B), and requires approximately 50-100 patients to estimate a preference model with acceptable precision for all parameters. (3) Therefore, the aim was to recruit 80-100 patients.

Statistical Plan

An analysis was performed of 115 PWHA (mean age 37 years, range 18-70), 115 PWHA completed 12 DCE and 12 DCE_{TO} tasks. Choices were analyzed using conditional logistic models. Socio-demographic data, clinical characteristics and EQ-5D-5L were obtained from medical records or were self-reported. Once the patients completed the survey, data was analyzed, and the relative preference weight for each attribute level was estimated. The relative preference of treatment attributes was analyzed using conditional logistic models in STATA 16 (Timberlake Consultants Limited, Richmond upon Thames, UK). Relative preference weights

were estimated, with 95% confidence intervals (CIs), and odds ratios (ORs) were derived from these estimates.

Separate models were fitted with and without TTO values as a treatment attribute. Fitting a model excluding TTO values allowed for the preferences of non-TTO attributes to be examined, without the influence of TTO values. The mixed logit estimating equation without TTO is $V = \beta_1 \times \text{Frequency/Mode of administration} + \beta_2 \times \text{Mental health} + \beta_3 \times \text{Pain} + \beta_4 \times \text{Annual Bleeds}$.

DCE_{TTO} Health Utility Calculations

Fitting an additional model including TTO values, acts as a utility elicitation analysis to examine the extent to which TTO values influenced the preference weights of the coreHEM attributes. In the latter model, TTO values were included as a continuous variable. The conditional logit estimating equation with TTO is $V = \beta_1 \times \text{Frequency/Mode of administration} \times \text{life-years} + \beta_2 \times \text{Mental health} \times \text{life-years} + \beta_3 \times \text{Pain} \times \text{life-years} + \beta_4 \times \text{Annual Bleeds} \times \text{life-years} + \beta_5 \times \text{TTO}$.

The objective here was to derive the mean utility value of state x_j based on the DCE that corresponds to a 20-year TTO value, which is $t/20$. The health state utility value estimate was implemented by assuming, as in TTO, that for each profile made up from living in state x_j for 200 years, there is a number of years ($t < 20$) in full health which generates the same level of utility. Thus, the probability of choosing the profile describing living in full health (11111) for 20 years is equal to the probability of choosing a profile describing living in a particular health state x_j for 20 years.

This was solved so that this value is expressed as a function of the regression estimates: TTO-based health utility was computed using the results of the model with TTO life year values

included. Time trade-off (with 95% CI) disutility was calculated for each treatment attribute level that was significant in the model, by dividing the model coefficient (relative preference weight) of the attribute level by the negative model coefficient of the TTO life years.

In summary, the disutility was derived by dividing the coefficient for the treatment attribute level with the coefficient for the life-year attribute as below.

The disutility for treatment attribute $i = \beta_i / \beta_5$

The annualized disutility for 20 TTO years = $\beta_i / (\beta_5 \times 20)$

An ordinary least squares (OLS) regression was also run on EQ-5D-5L utility scores and VAS, to examine the extent to which age, race, hemophilia severity, annual bleed rate and frequency of treatment, influenced these scores. The equation is $Y = \alpha + \beta_1 \times age + \beta_2 \times race + \beta_3 \times hemophilia\ severity + \beta_4 \times Annual\ Bleed\ Rate + \beta_5 \times Frequency\ of\ Treatment +$

Subgroup Analyses

DCE subgroup analyses was performed by age (<40, \geq 40), income (< \$25,000, \$25,000-\$49,999, \$50,000-\$74,999, \geq \$75,000), hemophilia severity (mild, moderate, severe), treatment frequency (\geq once a week, once every 2-4 weeks, > every 4 weeks (don't know)), and history of inhibitor vs non-inhibitor. And the following subgroups were also analyzed looking at EQ-5D-5L utility values: hemophilia severity (mild, moderate, severe), annual bleed rate (zero annual bleeds/don't know, 1-4 annual bleeds, \geq 5 annual bleeds), general health overall (excellent, very good, good, fair, poor), and frequency of treatment (treatment \geq once a week, treatment every 2-4 weeks, < 4 weeks or don't know). These groups were chosen by asking patients what is most important to them when thinking about their hemophilia.

RESULTS

We performed an analysis of 115 PWHA (mean age 37 years, range 18-70) who participated in a web-based or in-clinic survey, of these 115 PWHA completed 12 DCE and 12 DCE_{TO} tasks. All patients are adult male, and majority White (90%), have Medicaid (65%), are employed part-time (44%), have an annual income of \$50,000-\$74,999 (55%), and have some college education (43%) or a college degree (43%). Most patients have moderate disease (52%), with an annual bleed rate of 1-4 bleeds (70%). Many have had an inhibitor (70%), are on prophylaxis treatment (56%), are on long acting FVIII treatment (48%) and treat once every 4 weeks (42%). A few patients have or have had a central device, such as a port (11%), have had a joint procedure (17%), have joint problems (57%), have HIV (7%), and history of Hepatitis C (14%). When patients were asked about their general health in the past week, many stated good (61%) (Table 1). And lastly, approximately 57% reported that their treatment is moderately burdensome (Table 2).

Table 1: Demographic and clinical characteristics of patients

<i>Characteristic</i>	<i>Adult patients* (n=115)</i>
Age, years, Mean (SD)	37 (10.06)
<u>Race, Ethnicity</u> n (%)	
White	<u>103 (90)</u>
Black/African American	7 (6)
American Indian or Native Alaskan	0
Asian	3 (3)
Native Hawaiian or Other Pacific Islander	0
Other	1 (1)
Prefer Not to Answer	1 (1)
Hispanic or Latino/a	<u>75 (65)</u>
Non-Hispanic or Latino/a	37 (32)
Prefer Not to Answer	0
<u>Health insurance, n (%)</u>	
Commercial or Private	33 (29)
Medicaid	<u>75 (65)</u>
Medicare	4 (3)
None	1 (1)
Other	2 (2)

Employment status, n (%) **	
Working full-time	48 (42)
Part-time	<u>51 (44)</u>
Long Term Sick/Disability	2 (2)
Unemployed	8 (7)
Retired	4 (3)
Student full-time	4 (3)
Student part-time	1 (1)
Other	0
Prefer Not to Answer	2 (2)
Annual Income, n (%)	
< \$25,000	6 (5)
\$25,000-\$49,999	16 (14)
\$50,000-\$74,999	<u>63 (55)</u>
≥ \$75,000	22 (19)
Don't know	3 (3)
Prefer Not to Answer	5 (4)
Education level, n (%)	
High-School Diploma or Equivalent (e.g., GED)	9 (8)
Some college or 2-year degree (e.g., Associates, Vocational, Technical)	<u>49 (43)</u>
4-year college degree (e.g., Bachelors)	<u>49 (43)</u>
More than 4-year college degree (e.g., Masters, PhD, MD, etc.)	5 (4)
Prefer Not to Answer	3 (3)
Disease severity, n (%)	
Mild	19 (17)
Moderate	<u>60 (52)</u>
Severe	36 (31)
Don't know	0
Annual Bleed Rate, n (%)	
0	10 (9)
1-4 Bleeds	<u>81 (70)</u>
Greater than 5 Bleeds	23 (20)
Don't Know	1 (1)
FVIII inhibitors in the past, n (%)	
	81 (70)
Current treatment (at time of consent), n (%)	
On Demand	45 (39)
Prophylaxis	<u>64 (56)</u>
Other	3 (3)
None	1 (1)
Don't Know	2 (2)
Type of treatment (at time of consent), n (%)§§	
Bypassing Concentrate (e.g., Feiba)	2 (2)
Short-Acting FVIII	16 (14)
Long-Acting FVIII	<u>55 (48)</u>
Non-Factor Products (e.g., Emicizumab)	40 (35)
Other Products (e.g., Stimate)	1 (1)
None	1 (1)
Frequency of Treatment, n (%)	
More than once a week (2,3,4 times a week)	18 (16)
Once every week	7 (6)
Once every 2 weeks	31 (27)
Once every 4 weeks	<u>48 (42)</u>
Greater than 4 weeks (once every 5 or 6 weeks)	7 (6)

Don't Know

4 (3)

Previous/current use of central device, n (%)	13 (11)
Previous/Current Joint Procedure, n (%)	20 (17)
Previous/Current Joint Problems, n (%)	65 (57)
History of HIV, n (%)	8 (7)
History of Hepatitis C, n (%)	16 (14)
General health over the past 4 weeks, n (%)	
Excellent	11 (10)
Very Good	16 (14)
Good	<u>70 (61)</u>
Fair	18 (16)
Poor	0
*All were male HA, [†] Three patients work part-time and are full-time students, two patients work full-time and are full-time students, one patient works part-time and is retired	

Table 2: Burden of hemophilia treatment, n (%) Adult Patients (n=115)

<i>Not Burdensome at all</i>	12 (10%)
<i>Slightly Burdensome</i>	25 (22%)
<i>Moderately Burdensome</i>	66 (57%)
<i>Severely Burdensome</i>	11 (10%)
<i>Extremely Burdensome</i>	1 (1%)

In the DCE without TTO, with 5-year durability, most attributes were statistically significant with 5-year durability. Treatment administration was the most important attribute (2-3 times IV infusion per week vs. 5-year durability utility of -1.647), followed by mental health (always concerned vs. no concern utility of -1.368), bleeding (5 or more vs. none utility of -0.725), and finally chronic pain (yes vs. no utility of -0.355), except for occasionally concerned. For patients who are occasionally concerned (mental health), this attribute was not statistically significant, and there was no difference when compared to patients who are not concerned about their hemophilia, with 5-year durability (Table 3).

Table 3: DCE Treatment Attributes Without TTO, 5 yr. Durability

<i>Variable</i>	<i>Coefficient</i>	<i>SE</i>	<i>p-value</i>	<i>95% Confidence Interval</i>	
<i>Treatment</i>					
One-time IV infusion, 5 years	(reference)				
One-time IV infusion, 10 years	-0.341	0.088	<0.001	0.168	0.514
1-2 times SQ injection per month	-1.090	0.104	<0.001	-1.293	-0.886
2-3 times IV infusion per week	-1.647	0.101	<0.001	-1.845	-1.448
<i>Mental health</i>					
No concern about your hemophilia	(reference)				
Occasionally concerned about your hemophilia	-0.142	0.084	0.090	-0.307	0.022
Always concerned about your hemophilia	-1.368	0.082	<0.001	-1.530	-1.207
<i>Chronic pain</i>					
No	(reference)				
Yes	-0.355	0.058	<0.001	-0.468	-0.242
<i>Bleeding</i>					
None	(reference)				
1 - 4 times	-0.368	0.079	<0.001	-0.523	-0.214
5 or more	-0.725	0.075	<0.001	-0.872	-0.577

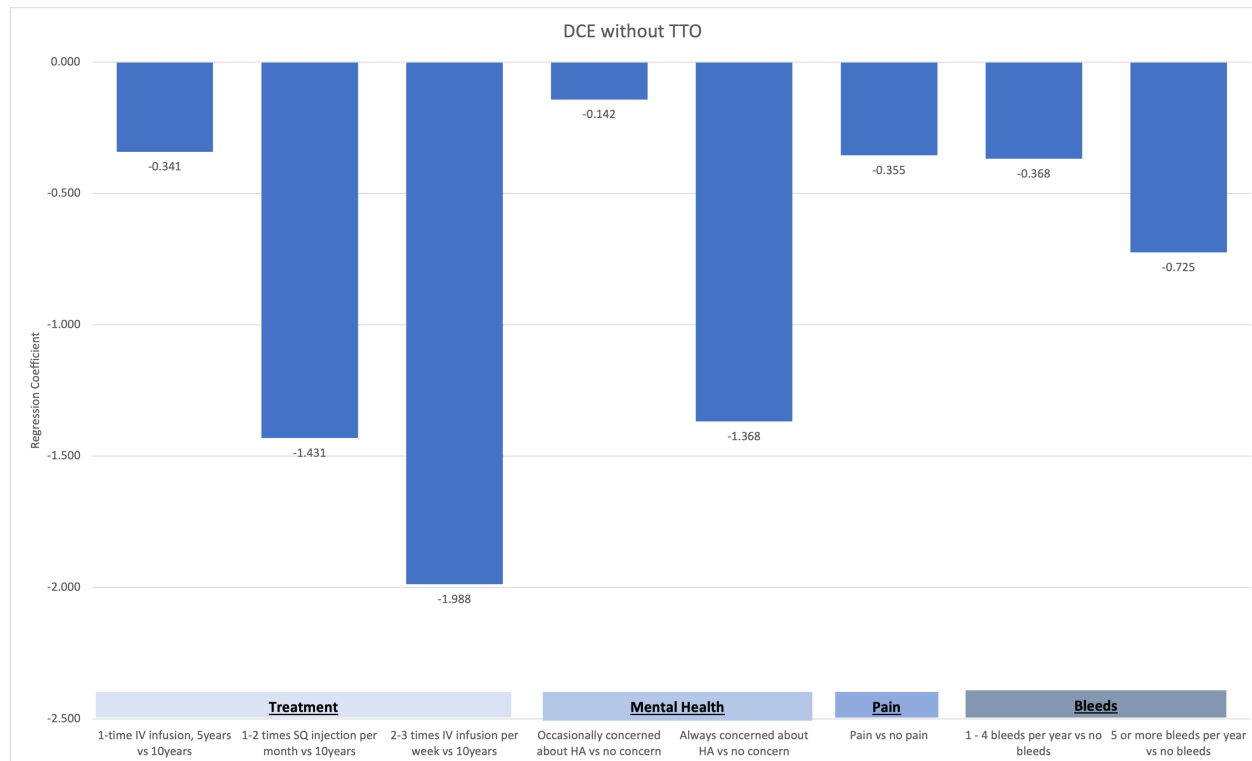
Once again in the DCE without TTO, with 10-year durability, most attributes were statistically significant. Treatment administration was the most important attribute (2-3 times IV infusion per week vs. 10-year durability utility of -1.99), followed by mental health (always concerned vs. no concern utility of -1.37), bleeding (5 or more vs. none utility of -0.73), and finally chronic pain (yes vs. no utility of -0.36). And again, in patients who are occasionally concerned (mental health), this attribute was not statistically significant, and there was no difference when compared to patients who are not concerned about their hemophilia, with 10-year durability (Table 4).

Table 4: DCE Treatment Attributes Without TTO, 10 yr. durability

<i>Variable</i>	<i>Coefficient</i>	<i>SE</i>	<i>p-value</i>	<i>95% Confidence Interval</i>	
<i>Treatment</i>					
One-time IV infusion, 10 years	(reference)				
One-time IV infusion, 5years	-0.341	0.088	<0.001	-0.514	-0.168
1-2 times SQ injection per month	-1.431	0.105	<0.001	-1.637	-1.225
2-3 times IV infusion per week	-1.988	0.101	<0.001	-2.186	-1.789
<i>Mental health</i>					
No concern about your hemophilia	(reference)				
Occasionally concerned about your hemophilia	-0.142	0.084	0.090	-0.307	0.022
Always concerned about your hemophilia	-1.368	0.082	<0.001	-1.530	-1.207
<i>Chronic pain</i>					
No	(reference)				
Yes	-0.355	0.058	<0.001	-0.468	-0.242
<i>Bleeding</i>					
None	(reference)				
1 - 4 times	-0.368	0.079	<0.001	-0.523	-0.214
5 or more	-0.725	0.075	<0.001	-0.872	-0.577

Overall, as shown in Figure 3, patient preferences based on the magnitude of the regression coefficient, is statistically significant when comparing at least one level of that attribute with the reference level.

Figure 3: Regression Coefficient-DCE on coreHEM attributes, 10yr durability



†Regression coefficient < 0 shows aversion to a treatment attribute”

When adding in the life duration attribute, DCE_{TTO}, most attributes were statistically significant with 5-year durability. Treatment administration was the most important attribute (2-3 times IV infusion per week vs. 5-year durability utility of -0.066), followed by mental health (always concerned vs. no concern utility of -0.061), bleeding (5 or more vs. none utility of -0.050), and finally chronic pain (yes vs. no utility of -0.002. For patients who are occasionally concerned (mental health), this attribute was not statistically significant, in addition to chronic pain (yes). There was not significant difference when compared to patients who are not concerned about their hemophilia, and those stating no pain, with 5-year durability (Table 5).

Table 5: DCE Treatment Attributes With TTO, 5 yr. Durability

<i>Variable</i>	<i>Coefficient</i>	<i>SE</i>	<i>p-value</i>	<i>95% Confidence Interval</i>	
<i>Treatment</i>					
One-time IV infusion, 5 years * years	(reference)				
One-time IV infusion, 10 years * years	0.040	0.007	<0.001	0.026	0.054
1-2 times SQ injection per month * years	-0.044	0.007	<0.001	-0.057	-0.030
2-3 times IV infusion per week * years	-0.066	0.007	<0.001	-0.079	-0.052
<i>Mental health</i>					
No concern about your hemophilia * years	(reference)				
Occasionally concerned about your hemophilia * years	0.011	0.006	0.081	-0.001	0.023
Always concerned about your hemophilia * years	-0.061	0.005	<0.001	-0.071	-0.050
<i>Chronic pain</i>					
No * years	(reference)				
Yes * years	-0.002	0.004	0.660	-0.010	0.007
<i>Bleeding</i>					
None * years	(reference)				
1 - 4 times * years	-0.033	0.006	<0.001	-0.044	-0.022
5 or more * years	-0.050	0.006	<0.001	-0.063	-0.038
<i>Life Duration</i>	0.074	0.013	<0.001	0.048	0.099

Once again when with 10-year durability, with the life duration attribute, DCE_{TTO}, most attributes were statistically significant. Treatment administration was the most important attribute (2-3 times IV infusion per week vs. 10-year durability utility of -0.106), followed by mental health (always concerned vs. no concern utility of -0.061), bleeding (5 or more vs. none utility of -0.050), and finally chronic pain (yes vs. no utility of -0.002). For patients who chose yes for chronic pain, this attribute was not statistically significant. There was not significant difference when compared to patients stating no pain, with 10-year durability (Table 6).

Table 6: DCE Treatment Attributes With TTO, 10 yr. Durability

<i>Variable</i>	<i>Coefficient</i>	<i>SE</i>	<i>p-value</i>	<i>95% Confidence Interval</i>	
<i>Treatment</i>					
One-time IV infusion, 10 years * years	(reference)				
One-time IV infusion, 5 years * years	-0.040	0.007	<0.001	-0.054	-0.026
1-2 times SQ injection per month * years	-0.084	0.008	<0.001	-0.099	-0.069
2-3 times IV infusion per week * years	-0.106	0.008	<0.001	-0.121	-0.091
<i>Mental health</i>					
No concern about your hemophilia * years	(reference)				
Occasionally concerned about your hemophilia * years	0.011	0.006	<0.001	-0.001	0.023
Always concerned about your hemophilia * years	-0.061	0.005	<0.001	-0.071	-0.050
<i>Chronic pain</i>					
No * years	(reference)				
Yes * years	-0.002	0.004	0.660	-0.010	0.007
<i>Bleeding</i>					
None * years	(reference)				
1 - 4 times * years	-0.033	0.006	<0.001	-0.044	-0.022
5 or more * years	-0.050	0.006	<0.001	-0.063	-0.038
<i>Life Duration</i>	0.114	0.013	<0.001	0.089	0.139

In the DCE_{TTO}, looking at treatment attributes, with annualized disutility with 10-year reference, all attributes were statistically significant, except for chronic pain (Table 7).

And with an annualized disutility with 5-year reference, all attributes were statistically significant, except for once again chronic pain (Table 8).

Table 7: Annualized Disutility Decrement 10 Year Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
Treatment				
One-time IV infusion, 10 years * years	(reference)			
One-time IV infusion, 5 years * years	-0.040	-0.353	-0.018	<0.001
1-2 times SQ injection per month * years	-0.084	-0.737	-0.037	<0.001
2-3 times IV infusion per week * years	-0.106	-0.930	-0.046	<0.001
Mental health				
No concern about your hemophilia * years	(reference)			
Occasionally concerned about your hemophilia * years	0.011	0.096	0.005	<0.001
Always concerned about your hemophilia * years	-0.061	-0.531	-0.027	<0.001
Chronic pain				
No * years	(reference)			
Yes * years	-0.002	-0.017	-0.001	0.660
Bleeding				
None * years	(reference)			
1 - 4 times * years	-0.033	-0.291	-0.015	<0.001
5 or more * years	-0.050	-0.441	-0.022	<0.001

- *Disutility*=coefficient for treatment attribute/coefficient for life duration attribute*
- *Annualized disutility (20 TTO years) =coefficient for treatment attribute/ (coefficient for life duration attribute *20)*

Table 8: Annualized Disutility Decrement 5 Year Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
Treatment				
One-time IV infusion, 5 years * years	(reference)			
One-time IV infusion, 10 years * years	0.040	0.545	0.027	<0.001
1-2 times SQ injection per month * years	-0.044	-0.591	-0.030	<0.001
2-3 times IV infusion per week * years	-0.066	-0.888	-0.044	<0.001
Mental health				
No concern about your hemophilia * years	(reference)			
Occasionally concerned about your hemophilia * years	0.011	0.149	0.007	<0.001
Always concerned about your hemophilia * years	-0.061	-0.819	-0.041	<0.001
Chronic pain				
No * years	(reference)			
Yes * years	-0.002	-0.025	-0.001	0.660
Bleeding				
None * years	(reference)			
1 - 4 times * years	-0.033	-0.448	-0.022	<0.001
5 or more * years	-0.050	-0.679	-0.034	<0.001

- *Disutility*=coefficient for treatment attribute/coefficient for life duration attribute*
- *Annualized disutility (20 TTO years) =coefficient for treatment attribute/ (coefficient for life duration attribute *20)*

When comparing both DCE_{TTO} with 10-year vs 5-year annualized utility decrement, there were slight differences, particularly on treatment administration. With emphasis on treatment administration, in the DCE_{TTO}, treatment with multiple IV infusions weekly was associated with an annualized utility decrement (0.046 vs. 10-year durability, 0.044 vs. 5-year). Treatment with multiple SQ injections monthly was associated with an annualized utility decrement (0.037 vs. 10-year durability, 0.030 vs. 5-year) (Table 9).

Table 9. DCE_{TTO} Annualized Utility Decrement

<u>10yr Durability (multiple IV weekly infusions)</u>	<u>0.046</u>
<u>5yr Durability (multiple IV weekly infusions)</u>	<u>0.044</u>
<u>10yr Durability (multiple SQ monthly injections)</u>	<u>0.037</u>
<u>5yr Durability (multiple SQ monthly injections)</u>	<u>0.030</u>

In the EQ-5D-5L, the mean EQ-5D -5L VAS was 75 and mean EQ-5D-5L utility score was 0.684. An ordinary least squares (OLS) regression was performed, with EQ-5D-5L utility scores (Table 10) and VAS scores (Table 11) to examine age, race, hemophilia severity, annual bleed rate and frequency of treatment. For both regressions, majority of the attributes were not statistically significant. EQ-5D-5L utility scores and VAS scores are not sensitive, therefore using EQ-5D-5L does not work for the chosen DCE attributes.

Table 10: OLS Regression EQ-5D-5L Utility Score

<i>Variable</i>	<i>Coefficient</i>	<i>SE</i>	<i>t</i>	<i>p-value</i>	<i>95% Confidence Interval</i>	
EQ-5D-5L Utility Score						
Age						
<40	(reference)					
≥ 40	-0.050	0.029	-1.74	0.085	-0.108	0.007
Race						
(White)	(reference)					
Black	0.172	0.055	3.12	0.002	0.063	0.282
American Indian or Native American	0	0	0	0	0	0
Asian	0.056	0.087	0.64	0.521	-0.117	0.229
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
Other	-0.291	0.145	-2.00	0.048	-0.579	-0.002
Prefer Not to Answer	0.201	0.134	1.50	0.137	-0.065	0.468
Hemophilia Severity						
Mild	(reference)					
Moderate	-0.030	0.040	-0.74	0.458	-0.110	0.050
Severe	0.007	0.063	0.11	0.915	-0.118	0.131
Annual Bleed Rate						
Zero	(reference)					
1-4 Bleeds	-0.166	0.057	-2.90	0.005	-0.279	-0.052
≥ 5	-0.267	0.062	-4.29	0.000	-0.390	-0.143
Don't know	-0.005	0.162	-0.03	0.978	-0.326	0.317
Frequency of Treatment						
> once a week, 2,3,4 times a week	(reference)					
Once every week	-0.154	0.062	-2.49	0.014	-0.276	-0.031
Once every 2 weeks	-0.058	0.058	-0.99	0.327	-0.174	0.058
Once every 4 weeks	-0.059	0.061	-0.97	0.335	-0.180	0.062
Greater than 4 weeks (once every 5 or 6 weeks)	0.055	0.073	0.75	0.457	-0.091	0.201
Don't know	0.077	0.096	0.80	0.423	-0.113	0.267

Table 11: OLS Regression EQ-5D-5L VAS Score

<i>Variable</i>	<i>Coefficient</i>	<i>SE</i>	<i>t</i>	<i>p-value</i>	<i>95% Confidence Interval</i>	
EQ-5D-5L VAS Score						
Age						
<40	(reference)					
≥ 40	-5.256	2.432	-2.16	0.033	-10.083	-0.430
Race						
White	(reference)					
Black	1.636	4.633	0.35	0.725	-7.556	10.828
American Indian or Native American	0	0	0	0	0	0
Asian	11.066	7.303	1.52	0.133	-3.426	25.557
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	0
Other	-19.154	12.202	-1.57	0.120	-43.365	5.057
Prefer Not to Answer	-14.473	11.273	-1.28	0.202	-36.840	7.894
Hemophilia Severity						
Mild	(reference)					
Moderate	-2.271	3.386	-0.67	0.504	-8.989	4.448
Severe	-6.162	5.269	-1.17	0.245	-16.617	4.293
Annual Bleed Rate						
Zero	(reference)					
1-4 Bleeds	-11.258	4.790	-2.35	0.021	-20.762	-1.754
≥ 5	-12.925	5.219	-2.48	0.015	-23.281	-2.569
Don't know	14.550	13.591	1.07	0.287	-12.417	41.516
Frequency of Treatment						
> once a week, 2,3,4 times a week	(reference)					
Once every week	-10.561	5.168	-2.04	0.044	-20.815	-0.307
Once every 2 weeks	-2.790	4.905	-0.57	0.571	-12.524	6.943
Once every 4 weeks	-0.681	5.126	-0.13	0.895	-10.851	9.490
Greater than 4 weeks (once every 5 or 6 weeks)	-7.717	6.164	-1.25	0.214	-19.947	4.514
Don't know	-17.232	8.048	-2.14	0.035	-33.200	-1.264

Subgroup Analyses

DCE_{TO}

In the subgroup analyses for DCE_{TO}, the results were mainly in line with the results from the overall sample. However, several differences were notable. When looking at patients with severe disease, income < \$25,000, income ≥ \$75,000, treatment ≥ once a week, and no

history of inhibitor, bleeding was the most important attribute, not treatment administration.

While all data analyses were analyzed and are shown in the tables section, the subgroups mainly focused on DCE without TTO 10 yr. durability, annualized disutility decrement 5 yr. reference and 10 yr. reference, which is the overall focus of the main DCE_{TTO}.

Age \geq 40 (n=38) (Tables 12, 13, 14, 15, 16, 17)

In the DCE, those patients \geq 40, treatment administration was the most important attribute (2-3 times IV per week, vs 10yr durability utility -1.840), mental health (always concerned vs. no concern utility of -1.032), bleeding (5 or more vs none utility of -0.890), and finally chronic pain (yes vs no utility -0.372). In the DCE_{TTO}, treatment with 2-3 times IV per week associated with an annualized utility decrement (0.037 vs 10yr durability, 0.031 vs. 5 yr.). Treatment with SQ injections per week with annualized utility decrement (0.029 vs 10yr, 0.019 vs 5 yr.).

Age < 40 (n=77) (Tables 18, 19, 20, 21, 22, 23)

In the DCE, those patients <40, treatment administration was the most important attribute (2-3 times IV per week, vs 10yr durability utility -2.086), mental health (always concerned vs. no concern utility of -1.551), bleeding (5 or more vs none utility of -0.648), and finally chronic pain (yes vs no utility -0.347). In the DCE_{TTO}, treatment with 2-3 times IV per week associated with an annualized utility decrement (0.051 vs 10yr durability, 0.052 vs. 5 yr.). Treatment with SQ injections per week with annualized utility decrement (0.040 vs 10yr, 0.035 vs 5 yr.).

Mild Severity (n=19) (Tables 24, 25, 26, 27, 28, 29)

In the DCE, those patients with mild disease severity, treatment administration was the most important attribute (2-3 times IV per week, vs 10yr durability utility -2.612), mental health (always concerned vs. no concern utility of -1.951), bleeding (5 or more vs none utility of -0.555), and finally chronic pain (yes vs no utility -0.330). In the DCE_{TTO}, treatment with 2-3 times IV per week associated with an annualized utility decrement (0.046 vs 10yr durability,

0.043 vs. 5 yr.). Treatment with SQ injections per week with annualized utility decrement (0.043 vs 10yr, 0.037 vs 5 yr.).

Moderate Severity (n=60) (Tables 30, 31, 32, 33, 34, 35)

In the DCE, those patients with moderate disease severity, treatment administration was the most important attribute (2-3 times IV per week, vs 10yr durability utility -3.197), mental health (always concerned vs. no concern utility of -2.341), bleeding (5 or more vs none utility of -0.251), and finally chronic pain (yes vs no utility -0.199). In the DCE_{TT0}, treatment with 2-3 times IV per week associated with an annualized utility decrement (0.052 vs 10yr durability, 0.052 vs. 5 yr.). Treatment with SQ injections per week with annualized utility decrement (0.043 vs 10yr, 0.040 vs 5 yr.).

Severe Severity (n=36) (Tables 36, 37, 38, 39, 40, 41)

In the DCE, those patients with severe disease severity, bleeding was the most important attribute (5 or more vs none utility of -1.551), treatment administration (2-3 times IV per week, vs 10yr durability utility -1.095), mental health (always concerned vs. no concern utility of -0.755), and finally chronic pain (yes vs no utility -0.570). In the DCE_{TT0}, treatment with 2-3 times IV per week associated with an annualized utility decrement (0.019 vs 10yr durability, 0.009 vs. 5 yr.). Treatment with SQ injections per week with annualized utility decrement (0.005 vs 10yr, 0.008 vs 5 yr.). *This is NOT in line with the results of the overall sample. Bleeding is most important attribute, whereas treatment administration was most important in the overall sample.

History of Inhibitor (n=81) (Tables 42, 43, 44, 45, 46, 47)

In the DCE, in patients with history of inhibitors, treatment administration was the most important attribute (2-3 times IV infusion per week vs. 10-yr. durability utility of -2.772), mental health (always concerned vs. no concern utility of -2.125), bleeding (5 or more vs. none utility of -0.475), and finally chronic pain (yes vs. no utility of -0.211). In the DCE_{TT0}, treatment with

multiple IV infusions weekly was associated with an annualized utility decrement (0.050 vs. 10-yr. durability, 0.049 vs. 5-yr.). Treatment with multiple SQ injections monthly was associated with an annualized utility decrement (0.043 vs. 10-yr. durability, 0.040 vs. 5-yr.).

No Inhibitor (n=34) (Tables 48, 49, 50, 51, 52, 53)

In the DCE, in patients with no history of inhibitors, bleeding was the most important attribute (5 or more vs. none utility of -1.415), treatment administration was next (2-3 times IV infusion per week vs. 10-yr. durability utility of -1.317), mental health (always concerned vs. no concern utility of -0.639), , and finally chronic pain (yes vs. no utility of -0.611). In the DCE_{TTO}, treatment with multiple IV infusions weekly was associated with an annualized utility decrement (0.019 vs. 10-yr. durability, 0.012 vs. 5-yr.). Treatment with multiple SQ injections monthly was associated with an annualized utility decrement (0.000 vs. 10-yr. durability, 0.011 vs. 5-yr.).

*This is NOT in line with the results of the overall sample. Bleeding is most important attribute, whereas treatment administration was most important in the overall sample.

Treatment < 4 weeks, don't know (n=11) (Tables 54, 55, 56, 57, 58, 59)

In the DCE, those patients who treat once every 2-4 weeks, treatment administration was the most important attribute (2-3 times IV infusion per week vs 10-yr. durability utility of -2.406), bleeding (5 or more times a year vs none utility of -1.082), mental health (always concerned vs no concern utility of -0.465), and lastly chronic pain (yes vs no utility of -0.444). In the DCE_{TTO}, treatment administration with multiple IV infusions weekly was associated with an annualized utility decrement (0.021 vs 10-yr. durability, 0.017 vs 5 yr.). Treatment with multiple SQ injections monthly was associated with an annualized utility decrement (0.001 vs 10-yr. durability, 0.006 vs 5 yr.).

Treatment once every 2-4 weeks (n=79) (Tables 60, 61, 62, 63, 64, 65)

In the DCE, those patients who treat < than 4 weeks or don't know, treatment administration was the most important attribute (2-3 times IV infusion per week vs 10-yr.

durability utility of -2.720), mental health (always concerned vs no concern utility of -2.003), bleeding (5 or more times a year vs none utility of -0.335), and lastly chronic pain (yes vs no utility of -0.286). In the DCE_{TTO}, treatment administration with multiple IV infusions weekly was associated with an annualized utility decrement (0.050 vs 10-yr. durability, 0.050 vs 5 yr.). Treatment with multiple SQ injections monthly was associated with an annualized utility decrement (0.043 vs 10-yr. durability, 0.039 vs 5 yr.).

Treatment \geq once a week (n=25) (Tables 66, 67, 68, 69, 70, 71)

In the DCE, those patients who treated \geq once a week, bleeding was the most important attribute (5 or more vs none utility of -1.717), mental health (always concerned vs. no concern utility of -0.964), treatment administration (2-3 times IV per week, vs 10yr durability utility of -0.874), and finally chronic pain (yes vs no utility -0.560). In the DCE_{TTO}, treatment with multiple IV infusions weekly was associated with an annualized utility decrement (0.022 vs. 10-yr. durability, 0.014 vs. 5-yr.). Treatment with multiple SQ injections monthly was associated with an annualized utility decrement (0.011 vs. 10-yr. durability, 0.000 vs. 5-yr.). *This is NOT in line with the results of the overall sample. Bleeding is most important attribute, whereas treatment administration was most important in the overall sample.

Income \geq \$75,000 (n=22) (Tables 72, 73, 74, 75, 76, 77)

In the DCE, those patients with an income \geq \$75,000, bleeding was the most important attribute (5 or more vs none utility of -1.599), treatment administration (2-3 times IV per week, vs 10yr durability utility -1.259), mental health (always concerned vs. no concern utility of -0.981) and finally chronic pain (yes vs no utility -0.564). In the DCE_{TTO}, treatment with 2-3 times IV per week associated with an annualized utility decrement (0.035 vs 10yr durability, 0.030 vs. 5 yr.). Treatment with SQ injections per week with annualized utility decrement (0.021 vs 10yr, 0.013 vs 5 yr.). *This is NOT in line with the results of the overall sample. Bleeding is

most important attribute, whereas treatment administration was most important in the overall sample.

Income \$25,000-\$49,999 (n=16) (Tables 78, 79, 80, 81, 82, 83)

In the DCE, those patients with an income of \$25,000-\$49,999, treatment administration was the most important attribute (2-3 times IV per week, vs 10yr durability utility -2.922), mental health (always concerned vs. no concern utility of -1.612), chronic pain (yes vs no utility -0.532), and finally bleeding (5 or more vs none utility of -0.466) . In the DCE_{TTO} treatment with 2-3 times IV per week associated with an annualized utility decrement (0.043 vs 10yr durability, 0.041 vs. 5 yr.). Treatment with SQ injections per week with annualized utility decrement (0.021 vs 10yr, 0.013 vs 5 yr.).

Income \$50,000-\$74,999 (n=63) (Tables 84, 85, 86, 87, 88, 89)

In the DCE, those patients with an income of \$50,000-\$74,999, treatment administration was the most important attribute (2-3 times IV per week, vs 10yr durability utility -2.962), mental health (always concerned vs. no concern utility of -2.348), bleeding (5 or more vs none utility of -0.392), and finally chronic pain (yes vs no utility -0.140). In the DCE_{TTO}, treatment with 2-3 times IV per week associated with an annualized utility decrement (0.052 vs 10yr durability, 0.054 vs. 5 yr.). Treatment with SQ injections per week with annualized utility decrement (0.047 vs 10yr, 0.045 vs 5 yr.).

Income < \$25,000 (n=6) (Tables 90, 91, 92, 93, 94, 95)

In the DCE, those patients with an income < \$25,000, bleeding was the most important attribute (5 or more vs none utility of -1.489), treatment administration (2-3 times IV per week, vs 10yr durability utility -1.339), chronic pain (yes vs no utility -0.427) and finally, mental health (always concerned vs. no concern utility of -0.318). In the DCE_{TTO}, treatment with 2-3 times IV per week associated with an annualized utility decrement (0.027 vs 10yr durability, 0.020 vs. 5 yr.). Treatment with SQ injections per week with annualized utility decrement (0.006 vs 10yr,

0.008 vs 5 yr.). *This is NOT in line with the results of the overall sample. Bleeding is most important attribute, whereas treatment administration was most important in the overall sample.

EQ-5D-5L

In the overall sample, the mean EQ-5D-5L VAS was 75 and mean EQ-5D-5L utility score was 0.684. In the subgroup analyses for EQ-5D-5L, once again the results were mainly consistent with the overall sample, but two groups stood out. In patients who have severe disease, the mean EQ-5D-5L was 73 and the utility score was 0.853. And in patients who treat their disease \geq once a week, the mean EQ-5D-5L was 72 and the utility score 0.878.

Disease Severity

In patients with mild disease (n=19), the mean EQ-5D-5L VAS was 78 and mean EQ-5D-5L utility score was 0.683. In patients with moderate disease (n=60), the mean EQ-5D-5L VAS was 75 and mean EQ-5D-5L utility score was 0.583. And in patients with severe disease (n=36), the mean EQ-5D-5L VAS was 73 and mean EQ-5D-5L utility score was 0.853.

Annual Bleed Rate

In patients with an annual bleed rate of zero/don't know (n=11), the mean EQ-5D-5L VAS was 81 and mean EQ-5D-5L utility score was 0.882. In patients with an annual bleed rate of 1-4 (n=81), the mean EQ-5D-5L VAS was 75 and mean EQ-5D-5L utility score was 0.635. And in patients with an annual bleed rate of ≥ 5 (n=23), the mean EQ-5D-5L VAS was 71 and mean EQ-5D-5L utility score was 0.763.

General Health Overall

In patients with excellent general health (n=11), the mean EQ-5D-5L VAS was 90 and mean EQ-5D-5L utility score was 0.883. In patients with very good general health (n=16), the mean EQ-5D-5L VAS was 81 and mean EQ-5D-5L utility score was 0.708. In patients with good general health (n=70), the mean EQ-5D-5L VAS was 74 and mean EQ-5D-5L was 0.603.

In patients with fair general health (n=18), the mean EQ-5D-5L VAS was 65 and mean EQ-5D-5L was 0.859. And there were no (0) patients with poor general health.

Frequency of Treatment

In patients with who treated themselves \geq once a week (2, 3, 4, times a week) (n=25), the mean EQ-5D-5L VAS was 72 and mean EQ-5D-5L utility score was 0.878. In patients who treated themselves once every 2-4 weeks (n=79), the mean EQ-5D-5L VAS was 77 and mean EQ-5D-5L utility score was 0.611. And in patients who treated themselves > 4 weeks (once every 5 or 6 weeks) or don't know how often they treat (n=11), the mean EQ-5D-5L VAS was 69 and mean EQ-5D-5L was 0.772.

DISCUSSION

1. Summary of study findings

DCE attributes leveraged the coreHEM framework for gene therapy, which was developed by a multi-stakeholder patient-led task force. This is a major strength for this study, and the first time a study such as this one, has been conducted. The combined use of DCE and TTO provides a new approach to measuring health utility of hemophilia treatment administration. Patients with hemophilia indicated that all coreHEM outcomes are important for treatment choices, but those of most importance based on the findings of this DCE_{TTO} demonstrate that when patients with hemophilia think of their disease, treatment administration is the most important attribute, followed by mental health, bleeding, and chronic pain.

The frequency of treatment administration, IV or SQ, and how often, is ultimately a deciding factor. Patients prefer a one-time IV treatment over repeated prophylactic administration. Repeated prophylactic treatment presents a burden to patients with hemophilia, including sticking themselves repeatedly, taking time out of their schedule in order to infuse, and dealing with “shotty” veins. And after speaking with patients, some stated that if they could get

a few years without sticking themselves, their disease would be more tolerable, and their quality of life better. This implies that the durability of the one-time IV treatment impacts the incremental utility improvement; patients with hemophilia are willing to trade life years to reduce treatment burden.

When looking at mental health in patients, optimal mental health would mean that patients with hemophilia are not concerned about their disease, but it was the 2nd most important attribute, revealing that majority of patients are always concerned about their disease. Mental health is a major deciding factor when considering treatment administration. With this being said, when patients were asked how burdensome their current hemophilia treatment is, majority stated that their treatment was moderately burdensome. Treatment burden isn't the only factor tied to mental health, but patients are also self-conscious, worry about day-to-day activities, have anxiety about bleeds, in addition to several other factors, when it comes to their hemophilia. Mental health also affects quality of life. Patients in this study, were also asked to complete the EQ-5D-5L and majority of the patients had slight problems with mobility, self-care, and anxiety and depression. Usual activities, and pain and discomfort, presented patients with moderate problems.

In addition, patients with hemophilia are constantly worried about bleeds. As a patient with hemophilia the blood is unable to clot, therefore the number of bleeds per year contributes to the severity of disease, in addition to how often the patient may have to administer treatment, and what type of treatment. Ultimately, patients would prefer no bleeds. The same for chronic pain, patients would prefer no pain, the pain that comes along with bleeds, treatment administration, and the overall burden of the disease.

When conducting subgroup analyses, the four groups that stood out were, patients with severe disease, income < \$25,000, income \geq \$75,000, treatment \geq once a week, and no history of inhibitor. In these groups, bleeding was the most important attribute. In patients with severe disease and who treat \geq once a week, their disease is severe mainly due to bleeding and then factor VIII levels. Bleeding means more treatment, which is why they treat more than once a week, in order to prevent a bleed. It is assumed in patients with an income < \$25,000 bleeding is most important, because this means more treatments, more visits to the doctor's office and more resources, which requires more money. These patients do not want a bleed for this purpose. In patients with income \geq \$75,000, it is assumed that they do not want to spend additional income on treatments, if there is a bleed, they will need to contribute cost of treating a bleed, to the income they make. And in patients with no history of inhibitor, if an inhibitor develops, this means that their current treatment is no working, putting them at more risk for bleeds.

In the EQ-5D-5L subgroup analyses, when looking at mean VAS and utility scores, the two groups that stood out were patients with severe disease and patients who treat \geq once a week. In both groups, their mean VAS and utility scores were quite high, meaning the closer to one, this represents perfect health. It is important to keep in mind that patients with severe disease are usually seen more often, or have more contact with the hemophilia team, and those who treat more than once a week, have more protection. This may be the reason for the higher EQ-5D-5L scores. This could also possibly be due to the disability paradox. Measuring the patient-reported impact of conditions with lasting disabilities, such as hemophilia, may include a counterintuitive phenomenon known as the 'disability paradox', where patients report good or excellent QoL while observers characterize the patients' daily struggles much less favorably (O'Hara et al.,

2021). This means that the patients have adapted to living with hemophilia and whatever struggles they may face.

In the EQ-5D-5L OLS regression with utility score and VAS score, both regressions were consistent, and shows that treatment process, such as annual bleed rate and frequency of treatment, can have an impact on quality of life, and health state utilities. While there are small differences, for both regressions, majority of the attributes were not statistically significant. EQ-5D-5L utility scores and VAS scores are not sensitive, therefore using EQ-5D-5L does not work for the chosen DCE attributes.

When looking at the EQ-5D-5L, and conducting a discrete choice experiment, it is important to keep in mind that measuring quality of life on hypothetical treatment attributes can be difficult. The treatment scenarios are utilized to give practitioners a better idea of what patients would like. In a perfect world, patients would like an excellent quality of life, but if a treatment is not readily available, EQ-5D-5L is difficult to measure. This is why it is important that coreHEM accounts for patient involvement, so that outcomes can be taken into consideration when considering new and upcoming treatments for hemophilia. In addition, is also important that ICER reported that coreHEM measures are good but miss some aspects of quality of life in patients with hemophilia. There can be a disability paradox in hemophilia: patients living with hemophilia who report that their health status is better than that of the average population. If population-based measures are used, rather than those directly assessed in patients with hemophilia, the quality of life for patients living with hemophilia may be misrepresented (ICER, 2022).

2. How did our findings compare to other studies?

There is no previous work with DCE_{TO}, while deriving the utility methods in hemophilia, this is the first study of this kind. Compared with other methods of treatment process, the DCE_{TO} framework was utilized to directly establish health utility values, to provide

a more efficient approach to addressing some of the challenges frequently encountered in health economic evaluation. The estimated utility value was consistent with the literature. In a study conducted by Rowan et al., (2021) in males with Duchenne Muscular Dystrophy (DMD), a rare inherited condition that predominantly affects boys. which causes muscle damage and progressive weakness. A DCE_{TTO} was performed, with DMD-QoL-8D as a quality-of-life measurement. Although, EQ-5D-3L or EQ-5D-5L is the recommended measurement, this study generated preference weights for the DMD-QoL-8D, a DMD specific Preference Based Measure (PBM) that can be used to generate utility values for people with DMD and can be used to inform cost-effectiveness analyses of interventions in DMD. In another study, which examined health states for large descriptive systems to explore stability of DCE_{TTO}, to estimate health utility values from the five-level EQ-5D, it was found that the DCE_{TTO} is a feasible method that produces generally logically consistent coefficients for larger descriptive systems such as EQ-5D-5L. And there is also evidence supporting important design features for future valuation studies that use the DCE_{TTO} (Bansback, Hole, Mulhern, & Tsuchiya, 2014). In a study by Rogers et al., (2022), looking at the valuation of Caries Impacts and Experiences Questionnaire for Children (CARIES-QC), an adolescent preference-based measure of dental caries (tooth decay), utilizing best-worst scaling (BWS) tasks for completion by adolescents, there was also a DCE-TTO developed for completion by adults over 18 years. This was conducted to generate utility values anchored on the 1-0 full-health-dead scale, and then map the BWS utility values onto the DCE-TTO utility values to generate adolescent utility values, which are required to generate data onto the Quality Adjusted Life Years (QALY). It was found that the adolescent and adult value sets were able to provide a utility for every health state defined by the CARIES-QC classification system. After validation, there was also the potential for the use of CARIES-

QC in determining the cost-effectiveness of interventions to improve children's oral health. In economic evaluations this measure can also be used to determine the most cost-effective pathways for managing children with caries, with the goal of reducing the number of general anesthetics required, while improving the quality and timing of those that are needed. And lastly, in a paper studying the need for a better dementia-specific preference-based instrument, found the DCE_{TTO} utility value set for the Alzheimer's Disease Five Dimensions (AD-5D) utility, classification system will have wide applicability in facilitating QALY calculations for the economic evaluation of treatments and interventions in people with dementia and their family/caregivers. The value set will assist both community and nursing home with interventions and can be used to inform future planning and resource allocation for dementia care (Comans et al., 2020).

When comparing other studies, while they are not focused on hemophilia, but other medical conditions, in addition to other quality of life measures, there is consistency when conducting a DCE_{TTO}. All preference-based measures have two common elements: a health state classification system that can be used to categorize all patients with the condition of interest and a means of obtaining a utility score for all states defined by the classification system (Comans et al., 2018). The framework does establish health utility values, which provide a more efficient approach to address some of the challenges frequently encountered in health economic evaluation. Particularly in this study, DCE attributes leveraged the coreHEM framework for gene therapy, which was developed by a multi-stakeholder patient-led task force. This combined use of DCE and TTO provides a new approach to measuring health utility of hemophilia treatment administration. Also based on data that was submitted to ICER (2022), Valoctocogene roxaparvovec was associated with a fixed utility gain per cycle as long as patients did not switch

therapies. Perhaps future studies should compare this approach with other approaches such as standard health utility measures, and vignette-based utility measures, and differences in patient preferences among subgroups (e.g., by severity, by treatment type).

3. Economic Concerns

Based on this study, it has been shown that a one-time IV treatment can provide important utility for PWHAs over currently available treatments, which is reflective of gene therapy. It is thought that gene therapy, can be administered one time and provide durable and potentially “curative” therapy for hemophilia, but with high price tags. The list or quoted prices of most cell therapies to date are in the range of \$4 million to \$1.0 million to \$2.0 million or more. These prices only represent acquisition or “upfront” costs, which may not include administration of the therapy, managing toxicities, tests and procedures, and additional hospital stays (Goodman, 2022).

Among studies reporting total annual health care expenditures of managing HA, the total health care costs per patient averaged from \$213,874 to \$869,940 (Chen et al., 2023). This amount is even more when accounting for patients with inhibitors who were treated with bypassing agents. The mean per-patient-per-month hemophilia-related total costs were on average for a patient with an inhibitor is \$57,232 vs no inhibitor \$11,899, higher medical costs with an inhibitor \$45,911 vs. no inhibitor \$10,352, and higher outpatient pharmacy costs with an inhibitor \$11,321 vs. no inhibitor \$1547 (Swindle et al., 2019). Based on 2010 Medicare spending, treatments for hemophilia are the costliest drug average per beneficiary (Guh et al., 2012). Lifelong treatment with factor-replacement therapy, either as prophylaxis or as acute or on-demand therapy, is the mainstay of hemophilia management. Spending on factor replacement

therapy makes up over 80% of the total direct expenditures for patients with hemophilia (Chen, 2016). These costs would need to be taken into consideration when thinking about gene therapy.

Fortunately, the 340B Drug Pricing Program (340B program), can lessen some of the cost burden on patients. This program aids in providing clotting factor and other drugs, used by patients in the hemophilia treatment center, to treat their bleeding disorders (HRSA, 2017). In addition, patients with insurance, private and government, have some form of hemophilia treatment coverage, when pertaining to factor-replacement therapy.

There are two gene therapies, which have recently been FDA approved. Hemgenix (etranacogene dezaparvovec), gene therapy for the treatment of adults with Hemophilia B (Factor IX deficiency), was approved on 11/22/22. Roctavian (valoctocogene roxaparvovec-rvox), was approved 6/29/2023, for patients with severe Hemophilia A (Factor VIII deficiency). Hemgenix has recently been added to payer coverage. The reimbursement guidelines have been published by CSL Behring, with very detailed and strict criteria (CSL Behring, 2022), meaning that patients will need to meet several inclusion factors, to qualify for coverage. Roctavian, which is manufactured by BioMarin does not have payer coverage yet.

According to the National Hemophilia Foundation (NHF), the current healthcare system is not equipped to handle large one-time payments. The new treatment options have short treatment regimens (one-time infusion) and benefits that create challenges. These challenges include uncertainty around how long the therapy will last and uncertainty around an individual remaining on a given insurance plan. In a study conducted by Limjoco et al. (2022), most patients expect the health system to cover gene therapy regardless of the cost, leading to the fact that funding structure for gene therapy will impact decision making, especially if there are direct patient costs. Overall, while gene therapy has been proven to be effective, there are still “lengthy

hoops to jump through” before it is a standard of care, and covered by insurance, such as the coverage for factor replacement therapy. Additionally, there will be a need for policy changes at the Federal level to enable coverage and access, and hopefully in the future covered under 340B.

4. Policy Considerations

Due to the novelty of gene therapy, there are currently no policies in place, where patients may get coverage. Gene therapy may bring sizeable benefits in high unmet-need areas, or life shortening conditions, and policy makers implemented several regulatory pathways to accelerate marketing authorization. This raised uncertainty when health technology assessment (HTA) agencies or payers attempted to understand the value of gene therapy. And because of the high costs of gene therapy, payers whether government or private insurers can be reluctant to support coverage (Drummand et al., 2019). While offering safe and efficacious vector products is top priority, issues for access not only include local or regional economics and national health policy, capability of acquiring or manufacturing vector at scale, medical infrastructure, acceptance by treaters and patients, buy-in of all stakeholders including regulatory bodies and healthcare financing and insurance systems, but also the hemophilia population (Reiss, Zhang, & Ohmori, 2021).

There has been one organization, The Institute for Clinical and Economic Review (ICER), who acknowledged that there is a need for policies in gene therapy. Therefore, they came together with various stakeholders to recommend policies, which was published in their December 2022 report. This is the first organization to come up with policy recommendations, unfortunately, there is very little data prior to this report that was published. The stakeholders consisted of two patients, two clinical experts, two payers, and two representatives from pharmaceutical manufacturers to discuss how best to apply the evidence to real-world practice

and policy. The recommendations were broken down into groups: payers, manufacturers, patient organizations, and researchers/regulators.

From the payer perspective, the best approach for US payers to address the uncertainty and high cost of gene therapies, is to work with manufacturers to develop and implement outcomes-based agreements. These agreements need to be in place, in case the outcome is failure, where payers should have no barriers in coverage for resuming their standard of care treatment for their hemophilia. There should also be inclusion and exclusion criteria for payers when considering treatment with gene therapy. It is not ideal that a patient with mild disease would be considered for gene therapy, whereas a patient with severe disease may be considered.

Manufacturers feel that the pricing of factor replacement therapies and of emicizumab, represents a failure of competition and is far too high. They feel this way, even considering the benefits of prophylaxis for patients, which creates financial toxicity for them and their families, for health systems, and builds a platform for pricing, for potential cures that will only exacerbate the problem. Solid steps by the federal government are needed to achieve prices more reasonably aligned with the benefit to the patient.

Patient organizations have two recommendations. The first, is that patient groups should continue to collaborate, to develop education materials that educate patients about the potential risks and benefits of gene therapies. And continue their work with other stakeholders to develop and disseminate evidence-based, balanced materials that are accessible to all patients, a shared decision-making approach. It is known that patient organizations, such as the National Bleeding Disorders Foundation, formerly known as the National Hemophilia Foundation, have a powerful voice, and should use this voice to create significant pressure for fair pricing and appropriate insurance coverage across all sectors of the health system. The finding that gene

therapy is cost effective does not mean it is affordable, that it will be accessible within the marketplace post-approval, or that it is an optimal treatment for every eligible patient.

Researcher and regulators feel that because of the novelty of gene therapy, there is lack of data about the long-term benefits and possible harms of the interventions, therefore patients who do receive gene therapy should be enrolled in long-term follow-up registries. In addition, regulators should require manufacturers to underwrite the cost of these registries. And the FDA should put in place a Risk Evaluation and Mitigation Strategy (REMS) which was requested by the National Hemophilia Foundation in July 2022.

Overall, all stakeholders agreed that the value of high-impact single and short-term therapies should not be determined exclusively by estimates of long-term cost offsets, particularly when the existing standard of care is acknowledged to be priced significantly higher than reasonable cost-effective levels. And policymakers should avoid using traditional cost-effectiveness analysis alone as a guide to considerations of fair pricing. While policies take time to implement, these recommendations will be passed on to pharmaceutical companies and US payers as independent input into their considerations around pricing and coverage. At the same time, patient advocates, physicians, US legislators, and international health technology assessment organizations have been referring to ICER's work, to better understand the balance of fair pricing and fair access.

5. Study Limitations

A limitation of this study is that the study sample was recruited from a single Hemophilia Treatment Center in Louisiana and NHF. We cannot generalize the results to other study settings. Also in other studies, when completing the DCE_{TTO} patients pick the treatment they prefer, but the TTO is phrased as a number of years, “then you die.” Whereas, in our study, “then you die”

was phrased as “remaining years of life” as it was thought stating it this way, would not be so “harsh” as using the word die.

It is important to keep in mind that this DCE_{TTO} is a hypothetical survey instrument. Patients were asked to pick their most preferred treatment preference, with attributes based on the coreHEM framework. The patients were asked to really think about what they were willing to trade off between treatment characteristics, and time. The study was explained to the patients, but there is also the concern of difficulties choosing which DCE_{TTO} was most preferred. Also due to the survey taking 20-25 minutes to complete there could have been fatigue.

This study also explored preferences in subgroups by age, disease severity, and income, with results generally being consistent with those for the overall population. However, the small sample sizes for some subgroups mean that the results should be interpreted with caution.

CONCLUSION

As stated earlier, this study was the first of this kind. Findings from DCEs may be used to inform drug development and support decision-making by healthcare professionals and payers. In the case of hemophilia, A, such findings can be used to inform stakeholders on whether PWHA prefer standard FVIII therapies or whether they prefer the treatment attributes offered by the non-factor therapies that have been approved more recently, such as gene therapy. The findings were utilized to make decisions in the ICER, Final Evidence Report, specifically for gene therapy in hemophilia A. This updated final study confirms the results from the pilot DCE-TTO study presented at EAHAD.

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SUBGROUP DCE-TTO TABLES

Table 12: AGE ≥ 40 DCE Treatment Attributes Without TTO, 5 yr. Durability

<i>Patients Older Than 40</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 5 years	(reference)					
One-time IV infusion, 10 years	0.295	0.156	1.890	0.058	-0.010	0.600
1-2 times SQ injection per month	-0.914	0.172	-5.320	<0.001	-1.251	-0.578
2-3 times IV infusion per week	-1.545	0.174	-8.900	<0.001	-1.885	-1.205
<i>Mental health</i>						
No concern	ref					
Occasionally Concerned	0.006	0.146	0.040	0.968	-0.279	0.291
Always Concerned	-1.032	0.134	-7.680	<0.001	-1.295	-0.768
<i>Chronic Pain</i>						
None	ref					
Yes	-0.372	0.100	-3.720	<0.001	-0.568	-0.176
<i>Bleeding</i>						
None	(reference)					
1-4 times	-0.416	0.136	-3.060	0.002	-0.682	-0.150
5 or more	-0.890	0.133	-6.690	<0.001	-1.151	-0.629

Table 13: AGE ≥ 40 DCE Treatment Attributes Without TTO, 10 yr. Durability

<i>Patients Older Than 40</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 10 years	(reference)					
One-time IV infusion, 5years	-0.295	0.156	-1.890	0.058	-0.600	0.010
1-2 times SQ injection per month	-1.209	0.177	-6.810	<0.001	-1.557	-0.861
2-3 times IV infusion per week	-1.840	0.172	-10.690	<0.001	-2.177	-1.502
<i>Mental Health</i>						
No concern	(reference)					
Occasionally Concerned	0.006	0.146	0.040	0.968	-0.279	0.291
Always Concerned	-1.032	0.134	-7.680	<0.001	-1.295	-0.768
<i>Chronic Pain</i>						
None	(reference)					
Yes	-0.372	0.100	-3.720	<0.001	-0.568	-0.176
<i>Bleeding</i>						
None	(reference)					
1 - 4 times	-0.416	0.136	-3.060	0.002	-0.682	-0.150
5 or more	-0.890	0.133	-6.690	<0.001	-1.151	-0.629

Table 14: AGE \geq 40 DCE Treatment Attributes With TTO, 5 yr. Durability

<i>Patients Older Than 40</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 5 years	(reference)					
One-time IV infusion, 10 years	0.037	0.013	2.890	0.004	0.012	0.062
1-2 times SQ injection per month	-0.030	0.012	-2.500	0.012	-0.053	-0.006
2-3 times IV infusion per week	-0.048	0.012	-3.890	<0.001	-0.072	-0.024
<i>Mental Health</i>						
No concern about your hemophilia	(reference)					
Occasionally concerned	0.014	0.011	1.250	0.213	-0.008	0.036
Always concerned about your hemophilia	-0.052	0.009	-5.710	<0.001	-0.070	-0.034
<i>Chronic Pain</i>						
No	(reference)					
Yes	-0.002	0.007	-0.240	0.812	-0.016	0.013
<i>Bleeding</i>						
None	(reference)					
1 - 4 times	-0.036	0.010	-3.630	<0.001	-0.056	-0.017
5 or more	-0.052	0.011	-4.670	<0.001	-0.074	-0.030
<i>Life Duration</i>	0.077	0.023	3.380	0.001	0.032	0.122

Table 15: AGE \geq 40 DCE Treatment Attributes With TTO, 10 yr. Durability

<i>Patients Older Than 40</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 10 years	(reference)					
One-time IV infusion, 5 years	-0.037	0.013	-2.890	0.004	-0.062	-0.012
1-2 times SQ injection per month	-0.066	0.013	-4.960	<0.001	-0.093	-0.040
2-3 times IV infusion per week	-0.084	0.013	-6.500	<0.001	-0.110	-0.059
<i>Mental Health</i>						
No concern about your hemophilia	(reference)					
Occasionally Concerned	0.014	0.011	1.250	0.213	-0.008	0.036
Always concerned about your hemophilia	-0.052	0.009	-5.710	<0.001	-0.070	-0.034
<i>Chronic Pain</i>						
No	(reference)					
Yes	-0.002	0.007	-0.240	0.812	-0.016	0.013
<i>Bleeding</i>						
None	(reference)					
1 - 4 times	-0.036	0.010	-3.630	<0.001	-0.056	-0.017
5 or more	-0.052	0.011	-4.670	<0.001	-0.074	-0.030
<i>Life Duration</i>	0.114	0.022	5.100	<0.001	0.070	0.158

Table 16: AGE ≥ 40 Annualized Disutility Decrement 5 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 5 years * years	(reference)			
One-time IV infusion, 10 years * years	0.037	0.479	0.024	0.004
1-2 times SQ injection per month * years	-0.030	-0.384	-0.019	0.012
2-3 times IV infusion per week * years	-0.048	-0.617	-0.031	<0.001
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally Concerned about your hemophilia * years	0.014	0.179	0.009	0.213
Always concerned about your hemophilia * years	-0.052	-0.673	-0.034	<0.001
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	-0.002	-0.023	-0.001	0.812
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.036	-0.471	-0.024	<0.001
5 or more * years	-0.052	-0.675	-0.034	<0.001

Disutility=coefficient for treatment attribute/coefficient for life duration attribute*

*Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)*

Table 17: AGE ≥ 40 Annualized Disutility Decrement 10 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 10 years * years	(reference)			
One-time IV infusion, 5 years * years	-0.037	-0.324	-0.016	0.004
1-2 times SQ injection per month * years	-0.066	-0.583	-0.029	<0.001
2-3 times IV infusion per week * years	-0.084	-0.741	-0.037	<0.001
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally concerned about your hemophilia * years	0.014	0.121	0.006	0.213
Always concerned about your hemophilia * years	-0.052	-0.455	-0.023	<0.001
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	-0.002	-0.016	-0.001	0.812
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.036	-0.318	-0.016	<0.001
5 or more * years	-0.052	-0.456	-0.023	<0.001

Disutility=coefficient for treatment attribute/coefficient for life duration attribute*

*Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)*

Table 18: AGE < 40 DCE Treatment Attributes Without TTO, 5 yr. Durability

<i>Patients < 40</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment Administration</i>						
One-time IV infusion, 5 years	(reference)					
One-time IV infusion, 10 years	0.367	0.108	3.400	0.001	0.156	0.578
1-2 times SQ injection per month	-1.191	0.132	-9.050	<0.001	-1.449	-0.933
2-3 times IV infusion per week	-1.719	0.126	-13.640	<0.001	-1.966	-1.472
<i>Mental health</i>						
none	(reference)					
Occasionally concerned about your hemophilia	-0.220	0.104	-2.130	0.033	-0.423	-0.017
Always concerned about your hemophilia	-1.551	0.106	-14.700	<0.001	-1.758	-1.344
<i>Chronic pain</i>						
None	(reference)					
Chronic Pain-Yes	-0.347	0.071	-4.900	<0.001	-0.485	-0.208
<i>Bleeding</i>						
none	(reference)					
1-4 times	-0.354	0.097	-3.630	<0.001	-0.545	-0.163
5 or more	-0.648	0.092	-7.010	<0.001	-0.829	-0.466

Table 19: AGE < 40 DCE Treatment Attributes Without TTO, 10 yr. Durability

<i>Patients < 40</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment administration</i>						
One-time IV infusion, 10 years	(reference)					
One-time IV infusion, 5years	-0.367	0.108	-3.400	0.001	-0.578	-0.156
1-2 times SQ injection per month	-1.557	0.132	-11.790	<0.001	-1.816	-1.299
2-3 times IV infusion per week	-2.086	0.126	-16.500	<0.001	-2.334	-1.838
<i>Mental health</i>						
none	ref					
Occasionally concerned about your hemophilia	-0.220	0.104	-2.130	0.033	-0.423	-0.017
Always concerned about your hemophilia	-1.551	0.106	-14.700	<0.001	-1.758	-1.344
<i>Chronic pain</i>						
none	ref					
yes	-0.347	0.071	-4.900	<0.001	-0.485	-0.208
<i>Bleeding</i>						
none	ref					
1-4 times	-0.354	0.097	-3.630	<0.001	-0.545	-0.163
5 or more	-0.648	0.092	-7.010	<0.001	-0.829	-0.466

Table 20: AGE < 40 DCE Treatment Attributes With TTO, 5 yr. Durability

<i>Patients < 40</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment administration</i>						
One-time IV infusion, 5 years * years	(reference)					
One-time IV infusion, 10 years * years	0.042	0.009	4.790	<0.001	0.025	0.060
1-2 times SQ injection per month * years	-0.051	0.008	-6.020	<0.001	-0.067	-0.034
2-3 times IV infusion per week * years	-0.075	0.009	-8.690	<0.001	-0.092	-0.058
<i>Mental health</i>						
No concern about your hemophilia * years	(reference)					
Occasionally concerned about your hemophilia * years	0.010	0.008	1.250	0.212	-0.005	0.025
Always concerned about your hemophilia * years	-0.065	0.007	-9.970	<0.001	-0.078	-0.053
<i>Chronic pain</i>						
No * years	(reference)					
Yes * years	-0.002	0.005	-0.420	0.675	-0.012	0.008
<i>Bleeding</i>						
None * years	(reference)					
1 - 4 times * years	-0.032	0.007	-4.470	<0.001	-0.045	-0.018
5 or more * years	-0.050	0.008	-6.480	<0.001	-0.065	-0.035
<i>Life Duration</i>	0.072	0.016	4.530	<0.001	0.041	0.104

Table 21: AGE < 40 DCE Treatment Attributes With TTO, 10 yr. Durability

<i>Patients < 40</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment administration</i>						
One-time IV infusion, 10 years * years	(reference)					
One-time IV infusion, 5 years * years	-0.042	0.009	-4.790	<0.001	-0.060	-0.025
1-2 times SQ injection per month * years	-0.093	0.010	-9.720	<0.001	-0.112	-0.074
2-3 times IV infusion per week * years	-0.117	0.009	-12.460	<0.001	-0.135	-0.099
<i>Mental health</i>						
No concern about your hemophilia * years	(reference)					
Occasionally concerned about your hemophilia * years	0.010	0.008	1.250	0.212	-0.005	0.025
Always concerned about your hemophilia * years	-0.065	0.007	-9.970	<0.001	-0.078	-0.053
<i>Chronic pain</i>						
No * years	(reference)					
Yes * years	-0.002	0.005	-0.420	0.675	-0.012	0.008
<i>Bleeding</i>						
None * years	(reference)					
1 - 4 times * years	-0.032	0.007	-4.470	<0.001	-0.045	-0.018
5 or more * years	-0.050	0.008	-6.480	<0.001	-0.065	-0.035
<i>Life Duration</i>	0.115	0.015	7.440	<0.001	0.084	0.145

Table 22: AGE < 40 Annualized Disutility Decrement 5 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment administration</i>				
One-time IV infusion, 5 years * years	(reference)			
One-time IV infusion, 10 years * years	0.042	0.587	0.029	<0.001
1-2 times SQ injection per month * years	-0.051	-0.703	-0.035	<0.001
2-3 times IV infusion per week * years	-0.075	-1.037	-0.052	<0.001
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally concerned about your hemophilia * years	0.010	0.133	0.007	0.212
Always concerned about your hemophilia * years	-0.065	-0.908	-0.045	<0.001
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	-0.002	-0.031	-0.002	0.675
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.032	-0.438	-0.022	<0.001
5 or more * years	-0.050	-0.691	-0.035	<0.001

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 23: AGE < 40 Annualized Disutility Decrement 10 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment administration</i>				
One-time IV infusion, 10 years * years	(reference)			
One-time IV infusion, 5 years * years	-0.042	-0.368	-0.018	<0.001
1-2 times SQ injection per month * years	-0.093	-0.809	-0.040	<0.001
2-3 times IV infusion per week * years	-0.117	-1.017	-0.051	<0.001
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally concerned about your hemophilia * years	0.010	0.083	0.004	0.212
Always concerned about your hemophilia * years	-0.065	-0.568	-0.028	<0.001
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	-0.002	-0.019	-0.001	0.675
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.032	-0.275	-0.014	<0.001
5 or more * years	-0.050	-0.432	-0.022	<0.001

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 24: Mild Severity DCE Treatment Attributes Without TTO, 5 yr. Durability

<i>Mild Severity</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment Administration</i>						
One-time IV infusion, 5 years	(reference)					
One-time IV infusion, 10 years	0.368	0.231	1.590	0.111	-0.084	0.820
1-2 times SQ injection per month	-1.590	0.321	-4.960	<0.001	-2.219	-0.961
2-3 times IV infusion per week	-2.244	0.312	-7.190	<0.001	-2.856	-1.632
<i>Mental Health</i>						
none	(reference)					
Occasionally concerned about your hemophilia	-0.120	0.233	-0.510	0.607	-0.576	0.336
Always concerned about your hemophilia	-1.951	0.255	-7.640	<0.001	-2.451	-1.451
<i>Chronic Pain</i>						
None	(reference)					
Chronic Pain-Yes	-0.330	0.152	-2.170	0.030	-0.628	-0.031
<i>Bleeding</i>						
none	(reference)					
1-4 times	-0.182	0.218	-0.840	0.403	-0.610	0.245
5 or more	-0.555	0.205	-2.710	0.007	-0.957	-0.154

Table 25: Mild Severity DCE Treatment Attributes Without TTO, 10 yr. Durability

<i>Mild Severity</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment Administration</i>						
One-time IV infusion, 10 years	ref					
One-time IV infusion, 5years	-0.368	0.231	-1.590	0.111	-0.820	0.084
1-2 times SQ injection per month	-1.958	0.311	-6.290	<0.001	-2.568	-1.348
2-3 times IV infusion per week	-2.612	0.304	-8.600	<0.001	-3.207	-2.017
<i>Mental Health</i>						
none	(reference)					
Occasionally concerned about your hemophilia	-0.120	0.233	-0.510	0.607	-0.576	0.336
Always concerned about your hemophilia	-1.951	0.255	-7.640	<0.001	-2.451	-1.451
<i>Chronic Pain</i>						
none	(reference)					
yes	-0.330	0.152	-2.170	0.030	-0.628	-0.031
<i>Bleeding</i>						
none	(reference)					
1-4 times	-0.182	0.218	-0.840	0.403	-0.610	0.245
5 or more	-0.555	0.205	-2.710	0.007	-0.957	-0.154

Table 26: Mild Severity DCE Treatment Attributes With TTO, 5 yr. Durability

<i>Mild Severity</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 5 years * years	(reference)					
One-time IV infusion, 10 years * years	0.068	0.019	3.530	<0.001	0.030	0.106
1-2 times SQ injection per month * years	-0.064	0.019	-3.340	0.001	-0.101	-0.026
2-3 times IV infusion per week * years	-0.074	0.019	-3.890	<0.001	-0.111	-0.037
<i>Mental health</i>						
No concern about your hemophilia * years	(reference)					
Occasionally concerned about your hemophilia * years	0.010	0.017	0.580	0.564	-0.023	0.043
Always concerned about your hemophilia * years	-0.100	0.015	-6.530	<0.001	-0.131	-0.070
<i>Chronic pain</i>						
No * years	(reference)					
Yes * years	0.009	0.012	0.740	0.459	-0.014	0.032
<i>Bleeding</i>						
None * years	(reference)					
1 - 4 times * years	-0.031	0.015	-1.990	0.046	-0.061	0.000
5 or more * years	-0.057	0.017	-3.390	0.001	-0.090	-0.024
<i>Life duration</i>	0.085	0.036	2.350	0.019	0.014	0.156

Table 27: Mild Severity DCE Treatment Attributes With TTO, 10 yr. Durability

<i>Mild Severity</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 10 years * years	(reference)					
One-time IV infusion, 5 years * years	-0.068	0.019	-3.530	<0.001	-0.106	-0.030
1-2 times SQ injection per month * years	-0.132	0.021	-6.160	<0.001	-0.174	-0.090
2-3 times IV infusion per week * years	-0.142	0.021	-6.810	<0.001	-0.183	-0.101
<i>Mental health</i>						
No concern about your hemophilia * years	(reference)					
Occasionally concerned about your hemophilia * years	0.010	0.017	0.580	0.564	-0.023	0.043
Always concerned about your hemophilia * years	-0.100	0.015	-6.530	<0.001	-0.131	-0.070
<i>Chronic pain</i>						
No * years	(reference)					
Yes * years	0.009	0.012	0.740	0.459	-0.014	0.032
<i>Bleeding</i>						
None * years	(reference)					
1 - 4 times * years	-0.031	0.015	-1.990	0.046	-0.061	0.000
5 or more * years	-0.057	0.017	-3.390	0.001	-0.090	-0.024
<i>Life Duration</i>	0.153	0.035	4.370	<0.001	0.085	0.222

Table 28: Mild Severity Annualized Disutility Decrement 5 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 5 years * years	(reference)			
One-time IV infusion, 10 years * years	0.068	0.799	0.040	<0.001
1-2 times SQ injection per month * years	-0.064	-0.748	-0.037	0.001
2-3 times IV infusion per week * years	-0.074	-0.869	-0.043	<0.001
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally concerned about your hemophilia * years	0.010	0.113	0.006	0.564
Always concerned about your hemophilia * years	-0.100	-1.178	-0.059	<0.001
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	0.009	0.103	0.005	0.459
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.031	-0.361	-0.018	0.046
5 or more * years	-0.057	-0.666	-0.033	0.001

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 29: Mild Severity Annualized Disutility Decrement 10 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 10 years * years	(reference)			
One-time IV infusion, 5 years * years	-0.068	-0.444	-0.022	<0.001
1-2 times SQ injection per month * years	-0.132	-0.860	-0.043	<0.001
2-3 times IV infusion per week * years	-0.142	-0.927	-0.046	<0.001
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally concerned about your hemophilia * years	0.010	0.063	0.003	0.564
Always concerned about your hemophilia * years	-0.100	-0.655	-0.033	<0.001
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	0.009	0.057	0.003	0.459
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.031	-0.201	-0.010	0.046
5 or more * years	-0.057	-0.370	-0.019	0.001

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute
Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute
*20)

Table 30: Moderate Severity DCE Treatment Attributes Without TTO, 5 yr. Durability

<i>Moderate Severity</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment Administration</i>						
One-time IV infusion, 5 years	(reference)					
One-time IV infusion, 10 years	0.756	0.141	5.350	<0.001	0.479	1.033
1-2 times SQ injection per month	-1.946	0.209	-9.310	<0.001	-2.356	-1.536
2-3 times IV infusion per week	-2.441	0.194	-12.600	<0.001	-2.821	-2.061
<i>Mental Health</i>						
none	(reference)					
Occasionally concerned about your hemophilia	-0.194	0.143	-1.360	0.175	-0.474	0.086
Always concerned about your hemophilia	-2.341	0.181	-12.950	<0.001	-2.695	-1.987
<i>Chronic Pain</i>						
None	(reference)					
Yes	-0.199	0.090	-2.210	0.027	-0.375	-0.023
<i>Bleeding</i>						
none	(reference)					
1-4 times	-0.204	0.135	-1.500	0.133	-0.469	0.062
5 or more	-0.251	0.126	-1.990	0.047	-0.498	-0.003

Table 31: Moderate Severity DCE Treatment Attributes Without TTO, 10 yr. Durability

<i>Moderate Severity</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment administration</i>						
One-time IV infusion, 10 years	(reference)					
One-time IV infusion, 5years	-0.756	0.141	-5.350	<0.001	-1.033	-0.479
1-2 times SQ injection per month	-2.702	0.208	-12.980	<0.001	-3.110	-2.294
2-3 times IV infusion per week	-3.197	0.202	-15.840	<0.001	-3.593	-2.802
<i>Mental Health</i>						
none	(reference)					
Occasionally concerned about your hemophilia	-0.194	0.143	-1.360	0.175	-0.474	0.086
Always concerned about your hemophilia	-2.341	0.181	-12.950	<0.001	-2.695	-1.987
<i>Chronic Pain</i>						
none	(reference)					
yes	-0.199	0.090	-2.210	0.027	-0.375	-0.023
<i>Bleeding</i>						
none	(reference)					
1-4 times	-0.204	0.135	-1.500	0.133	-0.469	0.062
5 or more	-0.251	0.126	-1.990	0.047	-0.498	-0.003

Table 32: Moderate Severity DCE Treatment Attributes With TTO, 5 yr. Durability

<i>Moderate Severity</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment administration</i>						
One-time IV infusion, 5 years	(reference)					
One-time IV infusion, 10 years	0.055	0.011	4.990	<0.001	0.033	0.076
1-2 times SQ injection per month	-0.092	0.011	-7.990	<0.001	-0.114	-0.069
2-3 times IV infusion per week	-0.120	0.012	-10.370	<0.001	-0.143	-0.098
<i>Mental health</i>						
none	(reference)					
Occasionally concerned about your hemophilia	0.011	0.010	1.090	0.275	-0.009	0.030
Always concerned about your hemophilia	-0.109	0.010	-11.130	<0.001	-0.128	-0.090
<i>Chronic pain</i>						
none	(reference)					
yes	0.014	0.007	1.940	0.052	0.000	0.028
<i>Bleeding</i>						
none	(reference)					
1-4 times	-0.020	0.009	-2.210	0.027	-0.037	-0.002
5 or more	-0.028	0.010	-2.830	0.005	-0.047	-0.008
<i>Life duration</i>	0.115	0.022	5.210	<0.001	0.072	0.159

Table 33: Moderate Severity DCE Treatment Attributes With TTO, 10 yr. Durability

<i>Moderate Severity</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment Administration</i>						
One-time IV infusion, 10 years	(reference)					
One-time IV infusion, 5years	-0.055	0.011	-4.990	<0.001	-0.076	-0.033
1-2 times SQ injection per month	-0.147	0.013	-11.360	<0.001	-0.172	-0.121
2-3 times IV infusion per week	-0.175	0.013	-13.690	<0.001	-0.200	-0.150
<i>Mental health</i>						
none	(reference)					
Occasionally concerned about your hemophilia	0.011	0.010	1.090	0.275	-0.009	0.030
Always concerned about your hemophilia	-0.109	0.010	-11.130	<0.001	-0.128	-0.090
<i>Chronic Pain</i>						
none	(reference)					
yes	0.014	0.007	1.940	0.052	0.000	0.028
<i>Bleeding</i>						
none	(reference)					
1-4 times	-0.020	0.009	-2.210	0.027	-0.037	-0.002
5 or more	-0.028	0.010	-2.830	0.005	-0.047	-0.008
<i>Life duration</i>	<i>0.170</i>	<i>0.022</i>	<i>7.830</i>	<i><0.001</i>	<i>0.127</i>	<i>0.213</i>

Table 34: Moderate Severity Annualized Disutility Decrement 5 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 5 years * years	(reference)			
One-time IV infusion, 10 years * years	0.055	0.476	0.024	<0.001
1-2 times SQ injection per month * years	-0.092	-0.797	-0.040	<0.001
2-3 times IV infusion per week * years	-0.120	-1.046	-0.052	<0.001
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally concerned about your hemophilia * years	0.011	0.093	0.005	0.275
Always concerned about your hemophilia * years	-0.109	-0.944	-0.047	<0.001
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	0.014	0.122	0.006	0.052
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.020	-0.172	-0.009	0.027
5 or more * years	-0.028	-0.240	-0.012	0.005

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 35: Moderate Severity Annualized Disutility Decrement 10 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 10 years * years	(reference)			
One-time IV infusion, 5 years * years	-0.055	-0.323	-0.016	<0.001
1-2 times SQ injection per month * years	-0.147	-0.863	-0.043	<0.001
2-3 times IV infusion per week * years	-0.175	-1.031	-0.052	<0.001
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally concerned about your hemophilia * years	0.011	0.063	0.003	0.275
Always concerned about your hemophilia * years	-0.109	-0.640	-0.032	<0.001
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	0.014	0.082	0.004	0.052
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.020	-0.116	-0.006	0.027
5 or more * years	-0.028	-0.162	-0.008	0.005

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 36: Severe Severity DCE Treatment Attributes Without TTO, 5 yr. Durability

<i>Severe Severity</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment Administration</i>						
One-time IV infusion, 5 years	(reference)					
One-time IV infusion, 10 years	-0.084	0.166	-0.510	0.612	-0.410	0.242
1-2 times SQ injection per month	-0.290	0.164	-1.760	0.078	-0.612	0.033
2-3 times IV infusion per week	-1.179	0.165	-7.160	<0.001	-1.502	-0.856
<i>Mental Health</i>						
None	(reference)					
Occasionally concerned about your hemophilia	-0.214	0.144	-1.490	0.136	-0.497	0.068
Always concerned about your hemophilia	-0.755	0.126	-5.970	<0.001	-1.002	-0.507
<i>Chronic Pain</i>						
none	(reference)					
yes	-0.570	0.102	-5.580	<0.001	-0.770	-0.370
<i>Bleeding</i>						
none	(reference)					
1-4 times	-0.725	0.135	-5.390	<0.001	-0.989	-0.461
5 or more	-1.551	0.147	-10.570	<0.001	-1.839	-1.264

Table 37: Severe Severity DCE Treatment Attributes Without TTO, 10 yr. Durability

<i>Severe Severity</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment administration</i>						
One-time IV infusion, 10 years	(reference)					
One-time IV infusion, 5years	0.084	0.166	0.510	0.612	-0.242	0.410
1-2 times SQ injection per month	-0.205	0.174	-1.180	0.237	-0.546	0.135
2-3 times IV infusion per week	-1.095	0.157	-6.960	<0.001	-1.403	-0.786
<i>Mental health</i>						
none	(reference)					
Occasionally concerned about your hemophilia	-0.214	0.144	-1.490	0.136	-0.497	0.068
Always concerned about your hemophilia	-0.755	0.126	-5.970	<0.001	-1.002	-0.507
<i>Chronic Pain</i>						
none	(reference)					
yes	-0.570	0.102	-5.580	<0.001	-0.770	-0.370
<i>Bleeding</i>						
none	(reference)					
1-4 times	-0.725	0.135	-5.390	<0.001	-0.989	-0.461
5 or more	-1.551	0.147	-10.570	<0.001	-1.839	-1.264

Table 38: Severe Severity DCE Treatment Attributes With TTO, 5 yr. Durability

<i>Severe Severity</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment administration</i>						
One-time IV infusion, 5 years	(reference)					
One-time IV infusion, 10 years	0.021	0.013	1.640	0.101	-0.004	0.047
1-2 times SQ injection per month	0.012	0.012	1.050	0.294	-0.011	0.035
2-3 times IV infusion per week	-0.013	0.012	-1.110	0.268	-0.037	0.010
<i>Mental health</i>						
none	(reference)					
Occasionally concerned about your hemophilia	0.008	0.011	0.770	0.441	-0.013	0.030
Always concerned about your hemophilia	-0.016	0.009	-1.790	0.073	-0.033	0.001
<i>Chronic pain</i>						
none	(reference)					
yes	-0.021	0.008	-2.770	0.006	-0.036	-0.006
<i>Bleeding</i>						
none	(reference)					
1-4 times	-0.055	0.010	-5.680	<0.001	-0.075	-0.036
5 or more	-0.084	0.011	-7.350	<0.001	-0.106	-0.061
<i>Life duration</i>	0.071	0.023	3.150	0.002	0.027	0.116

Table 39: Severe Severity DCE Treatment Attributes With TTO, 10 yr. Durability

<i>Severe Severity</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment administration</i>						
One-time IV infusion, 10 years	(reference)					
One-time IV infusion, 5 years	-0.021	0.013	-1.640	0.101	-0.047	0.004
1-2 times SQ injection per month	-0.009	0.013	-0.700	0.484	-0.035	0.017
2-3 times IV infusion per week	-0.035	0.012	-2.790	0.005	-0.059	-0.010
<i>Mental health</i>						
none	(reference)					
Occasionally concerned about your hemophilia	0.008	0.011	0.770	0.441	-0.013	0.030
Always concerned about your hemophilia	-0.016	0.009	-1.790	0.073	-0.033	0.001
<i>Chronic pain</i>						
none	(reference)					
yes	-0.021	0.008	-2.770	0.006	-0.036	-0.006
<i>Bleeding</i>						
none	(reference)					
1-4 times	-0.055	0.010	-5.680	<0.001	-0.075	-0.036
5 or more	-0.084	0.011	-7.350	<0.001	-0.106	-0.061
<i>Life duration</i>	0.093	0.023	4.010	<0.001	0.047	0.138

Table 40: Severe Severity Annualized Disutility Decrement 5 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 5 years * years	(reference)			
One-time IV infusion, 10 years * years	0.021	0.299	0.015	0.101
1-2 times SQ injection per month * years	0.012	0.169	0.008	0.294
2-3 times IV infusion per week * years	-0.013	-0.188	-0.009	0.268
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally concerned about your hemophilia * years	0.008	0.118	0.006	0.441
Always concerned about your hemophilia * years	-0.016	-0.218	-0.011	0.073
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	-0.021	-0.292	-0.015	0.006
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.055	-0.775	-0.039	<0.001
5 or more * years	-0.084	-1.171	-0.059	<0.001

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 41: Severe Severity Annualized Disutility Decrement 10 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 10 years * years	(reference)			
One-time IV infusion, 5 years * years	-0.021	-0.230	-0.011	0.101
1-2 times SQ injection per month * years	-0.009	-0.099	-0.005	0.484
2-3 times IV infusion per week * years	-0.035	-0.375	-0.019	0.005
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally concerned about your hemophilia * years	0.008	0.091	0.005	0.441
Always concerned about your hemophilia * years	-0.016	-0.168	-0.008	0.073
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	-0.021	-0.225	-0.011	0.006
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.055	-0.597	-0.030	<0.001
5 or more * years	-0.084	-0.901	-0.045	<0.001

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 42: Inhibitor DCE Treatment Attributes Without TTO, 5 yr. Durability

<i>Patients With Inhibitor</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 5 years	(reference)					
One-time IV infusion, 10 years	0.501	0.115	4.360	<0.001	0.276	0.726
1-2 times SQ injection per month	-1.832	0.169	-10.830	<0.001	-2.164	-1.501
2-3 times IV infusion per week	-2.271	0.157	-14.450	<0.001	-2.579	-1.963
<i>Mental health</i>						
No concern	(reference)					
Occasionally Concerned	-0.133	0.117	-1.140	0.253	-0.362	0.095
Always Concerned	-2.125	0.136	-15.580	<0.001	-2.392	-1.858
<i>Chronic Pain</i>						
None	(reference)					
Yes	-0.211	0.074	-2.850	0.004	-0.357	-0.066
<i>Bleeding</i>						
None	(reference)					
1-4 times	-0.230	0.110	-2.090	0.037	-0.445	-0.014
5 or more	-0.475	0.102	-4.660	<0.001	-0.675	-0.275

Table 43: Inhibitor DCE Treatment Attributes Without TTO, 10 yr. Durability

<i>Patients With Inhibitor</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 10 years	(reference)					
One-time IV infusion, 5years	-0.501	0.115	-4.360	<0.001	-0.726	-0.276
1-2 times SQ injection per month	-2.333	0.164	-14.220	<0.001	-2.654	-2.011
2-3 times IV infusion per week	-2.772	0.155	-17.840	<0.001	-3.076	-2.467
<i>Mental Health</i>						
No concern	(reference)					
Occasionally Concerned	-0.133	0.117	-1.140	0.253	-0.362	0.095
Always Concerned	-2.125	0.136	-15.580	<0.001	-2.392	-1.858
<i>Chronic Pain</i>						
None	(reference)					
Yes	-0.211	0.074	-2.850	0.004	-0.357	-0.066
<i>Bleeding</i>						
None	(reference)					
1 - 4 times	-0.230	0.110	-2.090	0.037	-0.445	-0.014
5 or more	-0.475	0.102	-4.660	<0.001	-0.675	-0.275

Table 44: Inhibitor DCE Treatment Attributes With TTO, 5 yr. Durability

<i>Patients With Inhibitor</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 5 years	(reference)					
One-time IV infusion, 10 years	0.057	0.009	6.110	<0.001	0.039	0.076
1-2 times SQ injection per month	-0.086	0.010	-8.810	<0.001	-0.105	-0.067
2-3 times IV infusion per week	-0.106	0.010	-10.970	<0.001	-0.125	-0.087
<i>Mental Health</i>						
No concern about your hemophilia	(reference)					
Occasionally concerned	0.011	0.008	1.320	0.186	-0.005	0.027
Always concerned about your hemophilia	-0.104	0.008	-13.050	<0.001	-0.119	-0.088
<i>Chronic Pain</i>						
No	(reference)					
Yes	0.011	0.006	1.920	0.055	0.000	0.023
<i>Bleeding</i>						
None	(reference)					
1 - 4 times	-0.027	0.008	-3.530	<0.001	-0.042	-0.012
5 or more	-0.042	0.008	-5.140	<0.001	-0.059	-0.026
<i>Life Duration</i>	0.108	0.018	5.870	<0.001	0.072	0.144

Table 45: Inhibitor DCE Treatment Attributes With TTO, 10 yr. Durability

<i>Patients With Inhibitor</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 10 years	(reference)					
One-time IV infusion, 5 years	-0.057	0.009	-6.110	<0.001	-0.076	-0.039
1-2 times SQ injection per month	-0.143	0.011	-13.210	<0.001	-0.164	-0.122
2-3 times IV infusion per week	-0.164	0.011	-15.400	<0.001	-0.184	-0.143
<i>Mental Health</i>						
No concern about your hemophilia	(reference)					
Occasionally Concerned	0.011	0.008	1.320	0.186	-0.005	0.027
Always concerned about your hemophilia	-0.104	0.008	-13.050	<0.001	-0.119	-0.088
<i>Chronic Pain</i>						
No	(reference)					
Yes	0.011	0.006	1.920	0.055	0.000	0.023
<i>Bleeding</i>						
None	(reference)					
1 - 4 times	-0.027	0.008	-3.530	<0.001	-0.042	-0.012
5 or more	-0.042	0.008	-5.140	<0.001	-0.059	-0.026
<i>Life Duration</i>	0.165	0.018	9.270	<0.001	0.130	0.200

Table 46: Inhibitor Annualized Disutility Decrement 5 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 5 years * years	(reference)			
One-time IV infusion, 10 years * years	0.057	0.530	0.026	<0.001
1-2 times SQ injection per month * years	-0.086	-0.793	-0.040	<0.001
2-3 times IV infusion per week * years	-0.106	-0.985	-0.049	<0.001
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally Concerned about your hemophilia * years	0.011	0.102	0.005	0.186
Always concerned about your hemophilia * years	-0.104	-0.962	-0.048	<0.001
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	0.011	0.106	0.005	0.055
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.027	-0.249	-0.012	<0.001
5 or more * years	-0.042	-0.393	-0.020	<0.001

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 47: Inhibitor Annualized Disutility Decrement 10 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 10 years * years	(reference)			
One-time IV infusion, 5 years * years	-0.057	-0.347	-0.017	<0.001
1-2 times SQ injection per month * years	-0.143	-0.865	-0.043	<0.001
2-3 times IV infusion per week * years	-0.164	-0.991	-0.050	<0.001
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally concerned about your hemophilia * years	0.011	0.066	0.003	0.186
Always concerned about your hemophilia * years	-0.104	-0.630	-0.031	<0.001
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	0.011	0.069	0.003	0.055
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.027	-0.163	-0.008	<0.001
5 or more * years	-0.042	-0.257	-0.013	<0.001

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 48: No Inhibitor DCE Treatment Attributes Without TTO, 5 yr. Durability

<i>Patients with No Inhibitor</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment administration</i>						
One-time IV infusion, 5 years	(reference)					
One-time IV infusion, 10 years	0.054	0.170	0.320	0.753	-0.279	0.386
1-2 times SQ injection per month	-0.330	0.165	-2.000	0.045	-0.653	-0.007
2-3 times IV infusion per week	-1.263	0.169	-7.480	<0.001	-1.594	-0.932
<i>Mental health</i>						
No concern	(reference)					
Occasionally Concerned	-0.230	0.149	-1.550	0.122	-0.521	0.062
Always Concerned	-0.639	0.129	-4.940	<0.001	-0.893	-0.385
<i>Chronic pain</i>						
None	(reference)					
Yes	-0.611	0.104	-5.870	<0.001	-0.815	-0.407
<i>Bleeding</i>						
None	(reference)					
1-4 times	-0.689	0.138	-5.000	<0.001	-0.960	-0.419
5 or more	-1.415	0.147	-9.640	<0.001	-1.703	-1.127

Table 49: No Inhibitor DCE Treatment Attributes Without TTO, 10 yr. Durability

<i>Patients With No Inhibitor</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 10 years	(reference)					
One-time IV infusion, 5years	-0.054	0.170	-0.320	0.753	-0.386	0.279
1-2 times SQ injection per month	-0.384	0.177	-2.170	0.030	-0.730	-0.038
2-3 times IV infusion per week	-1.317	0.166	-7.930	<0.001	-1.642	-0.991
<i>Mental Health</i>						
No concern	(reference)					
Occasionally Concerned	-0.230	0.149	-1.550	0.122	-0.521	0.062
Always Concerned	-0.639	0.129	-4.940	<0.001	-0.893	-0.385
<i>Chronic Pain</i>						
None	(reference)					
Yes	-0.611	0.104	-5.870	<0.001	-0.815	-0.407
<i>Bleeding</i>						
None	(reference)					
1 - 4 times	-0.689	0.138	-5.000	<0.001	-0.960	-0.419
5 or more	-1.415	0.147	-9.640	<0.001	-1.703	-1.127

Table 50: No Inhibitor DCE Treatment Attributes With TTO, 5 yr. Durability

<i>Patients With No Inhibitor</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 5 years	(reference)					
One-time IV infusion, 10 years	0.014	0.013	1.100	0.271	-0.011	0.040
1-2 times SQ injection per month	0.014	0.012	1.180	0.237	-0.009	0.036
2-3 times IV infusion per week	-0.015	0.012	-1.240	0.215	-0.039	0.009
<i>Mental Health</i>						
No concern about your hemophilia	(reference)					
Occasionally concerned	0.007	0.011	0.600	0.549	-0.015	0.028
Always concerned about your hemophilia	-0.012	0.009	-1.310	0.192	-0.029	0.006
<i>Chronic Pain</i>						
No	(reference)					
Yes	-0.020	0.008	-2.590	0.010	-0.034	-0.005
<i>Bleeding</i>						
None	(reference)					
1 - 4 times	-0.048	0.010	-4.890	<0.001	-0.068	-0.029
5 or more	-0.071	0.011	-6.210	<0.001	-0.093	-0.049
<i>Life Duration</i>	0.065	0.023	2.830	0.005	0.020	0.110

Table 51: No Inhibitor DCE Treatment Attributes With TTO, 10 yr. Durability

<i>Patients With No Inhibitor</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 10 years	(reference)					
One-time IV infusion, 5 years	-0.014	0.013	-1.100	0.271	-0.040	0.011
1-2 times SQ injection per month	-0.001	0.013	-0.060	0.955	-0.027	0.026
2-3 times IV infusion per week	-0.030	0.013	-2.330	0.020	-0.054	-0.005
<i>Mental Health</i>						
No concern about your hemophilia	(reference)					
Occasionally Concerned	0.007	0.011	0.600	0.549	-0.015	0.028
Always concerned about your hemophilia	-0.012	0.009	-1.310	0.192	-0.029	0.006
<i>Chronic Pain</i>						
No	(reference)					
Yes	-0.020	0.008	-2.590	0.010	-0.034	-0.005
<i>Bleeding</i>						
None	(reference)					
1 - 4 times	-0.048	0.010	-4.890	<0.001	-0.068	-0.029
5 or more	-0.071	0.011	-6.210	<0.001	-0.093	-0.049
<i>Life Duration</i>	0.079	0.023	3.430	0.001	0.034	0.125

Table 52: No Inhibitor Annualized Disutility Decrement 5 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 5 years * years	(reference)			
One-time IV infusion, 10 years * years	0.014	0.222	0.011	0.271
1-2 times SQ injection per month * years	0.014	0.210	0.011	0.237
2-3 times IV infusion per week * years	-0.015	-0.233	-0.012	0.215
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally Concerned about your hemophilia * years	0.007	0.103	0.005	0.549
Always concerned about your hemophilia * years	-0.012	-0.178	-0.009	0.192
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	-0.020	-0.301	-0.015	0.010
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.048	-0.743	-0.037	<0.001
5 or more * years	-0.071	-1.092	-0.055	<0.001

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 53: No Inhibitor Annualized Disutility Decrement 10 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 10 years * years	(reference)			
One-time IV infusion, 5 years * years	-0.014	-0.183	-0.009	0.271
1-2 times SQ injection per month * years	-0.001	-0.010	0.000	0.955
2-3 times IV infusion per week * years	-0.030	-0.375	-0.019	0.020
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally concerned about your hemophilia * years	0.007	0.084	0.004	0.549
Always concerned about your hemophilia * years	-0.012	-0.146	-0.007	0.192
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	-0.020	-0.248	-0.012	0.010
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.048	-0.612	-0.031	<0.001
5 or more * years	-0.071	-0.898	-0.045	<0.001

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 54: Treatment < 4 weeks DCE Treatment Attributes Without TTO, 5 yr. Durability

<i>Treat < than 4 weeks</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 5 years	(reference)					
One-time IV infusion, 10 years	0.083	0.302	0.270	0.785	-0.510	0.675
1-2 times SQ injection per month	-1.057	0.301	-3.510	<0.001	-1.647	-0.466
2-3 times IV infusion per week	-2.324	0.346	-6.720	<0.001	-3.001	-1.646
<i>Mental health</i>						
No concern	(reference)					
Occasionally Concerned	-0.096	0.282	-0.340	0.734	-0.648	0.457
Always Concerned	-0.465	0.246	-1.890	0.059	-0.947	0.018
<i>Chronic Pain</i>						
None	(reference)					
Yes	-0.444	0.188	-2.360	0.018	-0.812	-0.076
<i>Bleeding</i>						
None	(reference)					
1-4 times	-0.210	0.259	-0.810	0.417	-0.718	0.297
5 or more	-1.082	0.263	-4.110	<0.001	-1.598	-0.565

Table 55: Treatment < 4 weeks DCE Treatment Attributes Without TTO, 10 yr. Durability

<i>Treat < than 4 weeks</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 10 years	(reference)					
One-time IV infusion, 5 years	-0.083	0.302	-0.270	0.785	-0.675	0.510
1-2 times SQ injection per month	-1.139	0.332	-3.430	0.001	-1.790	-0.489
2-3 times IV infusion per week	-2.406	0.357	-6.750	<0.001	-3.105	-1.707
<i>Mental health</i>						
No concern	(reference)					
Occasionally Concerned	-0.096	0.282	-0.340	0.734	-0.648	0.457
Always Concerned	-0.465	0.246	-1.890	0.059	-0.947	0.018
<i>Chronic pain</i>						
None	(reference)					
Yes	-0.444	0.188	-2.360	0.018	-0.812	-0.076
<i>Bleeding</i>						
None	(reference)					
1-4 times	-0.210	0.259	-0.810	0.417	-0.718	0.297
5 or more	-1.082	0.263	-4.110	<0.001	-1.598	-0.565

Table 56: Treatment < 4 weeks DCE Treatment Attributes With TTO, 5 yr. Durability

<i>Treat < than 4 weeks</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 5 years	(reference)					
One-time IV infusion, 10 years	0.009	0.022	0.420	0.672	-0.034	0.053
1-2 times SQ injection per month	0.008	0.019	0.390	0.700	-0.031	0.046
2-3 times IV infusion per week	-0.023	0.021	-1.090	0.277	-0.063	0.018
<i>Mental health</i>						
No concern	(reference)					
Occasionally Concerned	0.006	0.019	0.320	0.746	-0.031	0.044
Always Concerned	-0.004	0.015	-0.260	0.797	-0.034	0.026
<i>Chronic Pain</i>						
None	(reference)					
Yes	-0.013	0.013	-1.020	0.306	-0.038	0.012
<i>Bleeding</i>						
None	(reference)					
1-4 times	-0.030	0.017	-1.780	0.074	-0.063	0.003
5 or more	-0.039	0.019	-2.010	0.044	-0.076	-0.001
<i>Life Duration</i>	0.067	0.039	1.710	0.088	-0.010	0.143

Table 57: Treatment < 4 weeks DCE Treatment Attributes With TTO, 10 yr. Durability

<i>Treat < than 4 weeks</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 10 years	(reference)					
One-time IV infusion, 5 years	-0.009	0.022	-0.420	0.672	-0.053	0.034
1-2 times SQ injection per month	-0.002	0.023	-0.080	0.933	-0.047	0.043
2-3 times IV infusion per week	-0.032	0.022	-1.450	0.147	-0.075	0.011
<i>Mental health</i>						
No concern	(reference)					
Occasionally Concerned	0.006	0.019	0.320	0.746	-0.031	0.044
Always Concerned	-0.004	0.015	-0.260	0.797	-0.034	0.026
<i>Chronic pain</i>						
None	(reference)					
Yes	-0.013	0.013	-1.020	0.306	-0.038	0.012
<i>Bleeding</i>						
None	(reference)					
1-4 times	-0.030	0.017	-1.780	0.074	-0.063	0.003
5 or more	-0.039	0.019	-2.010	0.044	-0.076	-0.001
<i>Life Duration</i>	0.076	0.039	1.980	0.048	0.001	0.152

Table 58: Treatment < 4 weeks Annualized Disutility Decrement 5 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 5 years * years	(reference)			
One-time IV infusion, 10 years * years	0.009	0.141	0.007	0.672
1-2 times SQ injection per month * years	0.008	0.112	0.006	0.700
2-3 times IV infusion per week * years	-0.023	-0.337	-0.017	0.277
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally Concerned about your hemophilia * years	0.006	0.092	0.005	0.746
Always concerned about your hemophilia * years	-0.004	-0.058	-0.003	0.797
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	-0.013	-0.195	-0.010	0.306
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.030	-0.451	-0.023	0.074
5 or more * years	-0.039	-0.577	-0.029	0.044

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 59: Treatment < 4 weeks Annualized Disutility Decrement 10 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 10 years * years	(reference)			
One-time IV infusion, 5 years * years	-0.009	-0.124	-0.006	0.672
1-2 times SQ injection per month * years	-0.002	-0.025	-0.001	0.933
2-3 times IV infusion per week * years	-0.032	-0.421	-0.021	0.147
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally concerned about your hemophilia * years	0.006	0.081	0.004	0.746
Always concerned about your hemophilia * years	-0.004	-0.051	-0.003	0.797
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	-0.013	-0.172	-0.009	0.306
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.030	-0.398	-0.020	0.074
5 or more * years	-0.039	-0.509	-0.025	0.044

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 60: Treatment Once every 2-4 weeks DCE Treatment Attributes Without TTO, 5 yr. Durability

<i>Treat Once Every 2-4 weeks</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 5 years	(reference)					
One-time IV infusion, 10 years	0.628	0.116	5.430	<0.001	0.401	0.854
1-2 times SQ injection per month	-1.525	0.154	-9.880	<0.001	-1.827	-1.222
2-3 times IV infusion per week	-2.092	0.147	-14.260	<0.001	-2.379	-1.804
<i>Mental health</i>						
No concern	(reference)					
Occasionally Concerned	-0.170	0.113	-1.500	0.134	-0.392	0.052
Always Concerned	-2.003	0.132	-15.130	<0.001	-2.262	-1.743
<i>Chronic pain</i>						
None	(reference)					
Yes	-0.286	0.076	-3.790	<0.001	-0.434	-0.138
<i>Bleeding</i>						
None	(reference)					
1-4 times	-0.301	0.108	-2.790	0.005	-0.513	-0.089
5 or more	-0.355	0.101	-3.500	<0.001	-0.554	-0.156

Table 61: Treatment Once every 2-4 weeks DCE Treatment Attributes Without TTO, 10 yr. Durability

<i>Treat Once Every 2-4 weeks</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 10 years	(reference)					
One-time IV infusion, 5 years	-0.628	0.116	-5.430	<0.001	-0.854	-0.401
1-2 times SQ injection per month	-2.152	0.155	-13.930	<0.001	-2.455	-1.849
2-3 times IV infusion per week	-2.720	0.152	-17.940	<0.001	-3.017	-2.422
<i>Mental health</i>						
No concern	(reference)					
Occasionally Concerned	-0.170	0.113	-1.500	0.134	-0.392	0.052
Always Concerned	-2.003	0.132	-15.130	<0.001	-2.262	-1.743
<i>Chronic pain</i>						
None	(reference)					
Yes	-0.286	0.076	-3.790	<0.001	-0.434	-0.138
<i>Bleeding</i>						
None	(reference)					
1-4 times	-0.301	0.108	-2.790	0.005	-0.513	-0.089
5 or more	-0.355	0.101	-3.500	<0.001	-0.554	-0.156

Table 62: Treatment Once every 2-4 weeks DCE Treatment Attributes With TTO, 5 yr. Durability

<i>Treat Once Every 2-4 weeks</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 5 years	(reference)					
One-time IV infusion, 10 years	0.057	0.009	6.010	<0.001	0.038	0.075
1-2 times SQ injection per month	-0.080	0.010	-8.260	<0.001	-0.099	-0.061
2-3 times IV infusion per week	-0.103	0.010	10.610	<0.001	-0.122	-0.084
<i>Mental health</i>						
No concern	(reference)					
Occasionally Concerned	0.013	0.008	1.500	0.134	-0.004	0.029
Always Concerned	-0.102	0.008	12.770	<0.001	-0.117	-0.086
<i>Chronic pain</i>						
None	(reference)					
Yes	0.014	0.006	2.260	0.024	0.002	0.025
<i>Bleeding</i>						
None	(reference)					
1-4 times	-0.028	0.008	-3.640	<0.001	-0.043	-0.013
5 or more	-0.042	0.008	-5.070	<0.001	-0.058	-0.026
<i>Life Duration</i>	0.103	0.018	5.610	<0.001	0.067	0.140

Table 63: Treatment Once every 2-4 weeks DCE Treatment Attributes With TTO, 10 yr. Durability

<i>Treat Once Every 2-4 weeks</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 10 years	(reference)					
One-time IV infusion, 5 years	-0.057	0.009	-6.010	<0.001	-0.075	-0.038
1-2 times SQ injection per month	-0.137	0.011	-12.660	<0.001	-0.158	-0.115
2-3 times IV infusion per week	-0.160	0.011	-15.030	<0.001	-0.181	-0.139
<i>Mental health</i>						
No concern	(reference)					
Occasionally Concerned	0.013	0.008	1.500	0.134	-0.004	0.029
Always Concerned	-0.102	0.008	-12.770	<0.001	-0.117	-0.086
<i>Chronic pain</i>						
None	(reference)					
Yes	0.014	0.006	2.260	0.024	0.002	0.025
<i>Bleeding</i>						
None	(reference)					
1-4 times	-0.028	0.008	-3.640	<0.001	-0.043	-0.013
5 or more	-0.042	0.008	-5.070	<0.001	-0.058	-0.026
<i>Life Duration</i>	0.160	0.018	8.950	<0.001	0.125	0.195

Table 64: Treatment Once every 2-4 weeks Annualized Disutility Decrement 5 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 5 years * years	(reference)			
One-time IV infusion, 10 years * years	0.057	0.551	0.028	<0.001
1-2 times SQ injection per month * years	-0.080	-0.776	-0.039	<0.001
2-3 times IV infusion per week * years	-0.103	-1.001	-0.050	<0.001
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally Concerned about your hemophilia * years	0.013	0.121	0.006	0.134
Always concerned about your hemophilia * years	-0.102	-0.987	-0.049	<0.001
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	0.014	0.131	0.007	0.024
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.028	-0.270	-0.014	<0.001
5 or more * years	-0.042	-0.409	-0.020	<0.001

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 65: Treatment Once every 2-4 weeks Annualized Disutility Decrement 10 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 10 years *	(reference)			
One-time IV infusion, 5 years * years	-0.057	-0.355	-0.018	<0.001
1-2 times SQ injection per month *	-0.137	-0.854	-0.043	<0.001
years				
2-3 times IV infusion per week *	-0.160	-0.999	-0.050	<0.001
years				
<i>Mental health</i>				
No concern about your hemophilia *	(reference)			
years				
Occasionally concerned about your hemophilia * years	0.013	0.078	0.004	0.134
Always concerned about your hemophilia * years	-0.102	-0.635	-0.032	<0.001
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	0.014	0.084	0.004	0.024
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.028	-0.174	-0.009	<0.001
5 or more * years	-0.042	-0.263	-0.013	<0.001

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 66: Treatment \geq Once a week DCE Treatment Attributes Without TTO, 5 yr.
Durability

<i>Treat ≥once a week</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 5 years	(reference)					
One-time IV infusion, 10 years	-0.093	0.206	-0.450	0.652	-0.496	0.311
1-2 times SQ injection per month	-0.270	0.208	-1.300	0.195	-0.678	0.138
2-3 times IV infusion per week	-0.967	0.200	-4.840	<0.001	-1.359	-0.575
<i>Mental health</i>						
No concern	(reference)					
Occasionally Concerned	-0.252	0.174	-1.450	0.148	-0.594	0.089
Always Concerned	-0.964	0.156	-6.200	<0.001	-1.269	-0.659
<i>Chronic pain</i>						
None	(reference)					
Yes	-0.560	0.127	-4.400	<0.001	-0.809	-0.311
<i>Bleeding</i>						
None	(reference)					
1-4 times	-0.771	0.164	-4.700	<0.001	-1.092	-0.450
5 or more	-1.717	0.186	-9.220	<0.001	-2.082	-1.352

Table 67: Treatment \geq Once a week DCE Treatment Attributes Without TTO, 10 yr.
Durability

<i>Treat \geq once a week</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 10 years	(reference)					
One-time IV infusion, 5 years	0.093	0.206	0.450	0.652	-0.311	0.496
1-2 times SQ injection per month	-0.177	0.214	-0.830	0.408	-0.596	0.242
2-3 times IV infusion per week	-0.874	0.187	-4.670	<0.001	-1.241	-0.507
<i>Mental health</i>						
No concern	(reference)					
Occasionally Concerned	-0.252	0.174	-1.450	0.148	-0.594	0.089
Always Concerned	-0.964	0.156	-6.200	<0.001	-1.269	-0.659
<i>Chronic pain</i>						
None	(reference)					
Yes	-0.560	0.127	-4.400	<0.001	-0.809	-0.311
<i>Bleeding</i>						
None	(reference)					
1-4 times	-0.771	0.164	-4.700	<0.001	-1.092	-0.450
5 or more	-1.717	0.186	-9.220	<0.001	-2.082	-1.352

Table 68: Treatment \geq Once a week DCE Treatment Attributes With TTO, 5 yr.**Durability**

<i>Treat \geq once a week</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 5 years	(reference)					
One-time IV infusion, 10 years	0.021	0.016	1.340	0.180	-0.010	0.051
1-2 times SQ injection per month	0.000	0.014	-0.030	0.978	-0.028	0.027
2-3 times IV infusion per week	-0.021	0.015	-1.430	0.153	-0.049	0.008
<i>Mental health</i>						
No concern	(reference)					
Occasionally Concerned	0.004	0.013	0.290	0.775	-0.022	0.030
Always Concerned	-0.021	0.010	-2.030	0.042	-0.042	-0.001
<i>Chronic pain</i>						
None	(reference)					
Yes	-0.027	0.009	-2.950	0.003	-0.044	-0.009
<i>Bleeding</i>						
None	(reference)					
1-4 times	-0.053	0.012	-4.480	<0.001	-0.076	-0.030
5 or more	-0.082	0.014	-6.050	<0.001	-0.109	-0.056
<i>Life Duration</i>	0.074	0.027	2.760	0.006	0.021	0.127

Table 69: Treatment \geq Once a week DCE Treatment Attributes With TTO, 10 yr.**Durability**

Treat \geq once a week	Coef.	Std. Err.	z	P> z	95% Conf.Interval	
<i>Treatment</i>						
One-time IV infusion, 10 years	(reference)					
One-time IV infusion, 5 years	-0.021	0.016	-1.340	0.180	-0.051	0.010
1-2 times SQ injection per month	-0.021	0.016	-1.340	0.180	-0.052	0.010
2-3 times IV infusion per week	-0.042	0.015	-2.790	0.005	-0.071	-0.012
<i>Mental health</i>						
No concern	(reference)					
Occasionally Concerned	0.004	0.013	0.290	0.775	-0.022	0.030
Always Concerned	-0.021	0.010	-2.030	0.042	-0.042	-0.001
<i>Chronic pain</i>						
None	(reference)					
Yes	-0.027	0.009	-2.950	0.003	-0.044	-0.009
<i>Bleeding</i>						
None	(reference)					
1-4 times	-0.053	0.012	-4.480	<0.001	-0.076	-0.030
5 or more	-0.082	0.014	-6.050	<0.001	-0.109	-0.056
<i>Life Duration</i>	0.095	0.027	3.460	0.001	0.041	0.149

Table 70: Treatment ≥ Once a week Annualized Disutility Decrement 5 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 5 years * years	(reference)			
One-time IV infusion, 10 years * years	0.021	0.282	0.014	0.180
1-2 times SQ injection per month * years	0.000	-0.005	0.000	0.978
2-3 times IV infusion per week * years	-0.021	-0.281	-0.014	0.153
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally Concerned about your hemophilia * years	0.004	0.051	0.003	0.775
Always concerned about your hemophilia * years	-0.021	-0.287	-0.014	0.042
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	-0.027	-0.359	-0.018	0.003
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.053	-0.711	-0.036	<0.001
5 or more * years	-0.082	-1.114	-0.056	<0.001

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 71: Treatment ≥ Once a week Annualized Disutility Decrement 10 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 10 years * years	(reference)			
One-time IV infusion, 5 years * years	-0.021	-0.220	-0.011	0.180
1-2 times SQ injection per month * years	-0.021	-0.224	-0.011	0.180
2-3 times IV infusion per week * years	-0.042	-0.439	-0.022	0.005
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally concerned about your hemophilia * years	0.004	0.040	0.002	0.775
Always concerned about your hemophilia * years	-0.021	-0.224	-0.011	0.042
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	-0.027	-0.280	-0.014	0.003
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.053	-0.554	-0.028	<0.001
5 or more * years	-0.082	-0.867	-0.043	<0.001

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 72: Income ≥ \$75,000 DCE Treatment Attributes Without TTO, 5 yr. Durability

<i>Income ≥ \$75,000</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment Administration</i>						
One-time IV infusion, 5 years	(reference)					
One-time IV infusion, 10 years	0.056	0.207	0.270	0.785	-0.349	0.462
1-2 times SQ injection per month	-0.801	0.226	-3.550	<0.001	-1.243	-0.358
2-3 times IV infusion per week	-1.542	0.219	-7.030	<0.001	-1.972	-1.112
<i>Mental health</i>						
none	(reference)					
Occasionally concerned about your hemophilia	-0.307	0.192	-1.600	0.109	-0.683	0.069
Always concerned about your hemophilia	-0.981	0.174	-5.650	<0.001	-1.321	-0.641
<i>Chronic Pain</i>						
None	(reference)					
Chronic Pain-Yes	-0.564	0.132	-4.270	<0.001	-0.824	-0.305
<i>Bleeding</i>						
none	(reference)					
1-4 times	-0.736	0.180	-4.090	<0.001	-1.089	-0.384
5 or more	-1.259	0.179	-7.040	<0.001	-1.609	-0.909

Table 73: Income ≥ \$75,000 DCE Treatment Attributes Without TTO, 10 yr. Durability

<i>Income ≥ \$75,000</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment Administration</i>						
One-time IV infusion, 10 years	(reference)					
One-time IV infusion, 5years	-0.056	0.207	-0.270	0.785	-0.462	0.349
1-2 times SQ injection per month	-0.857	0.230	-3.730	<0.001	-1.307	-0.407
2-3 times IV infusion per week	-1.599	0.216	-7.400	<0.001	-2.022	-1.175
<i>Mental health</i>						
none	(reference)					
Occasionally concerned about your hemophilia	-0.307	0.192	-1.600	0.109	-0.683	0.069
Always concerned about your hemophilia	-0.981	0.174	-5.650	<0.001	-1.321	-0.641
<i>Chronic pain</i>						
None	(reference)					
Chronic Pain-Yes	-0.564	0.132	-4.270	<0.001	-0.824	-0.305
<i>Bleeding</i>						
none	(reference)					
1-4 times	-0.736	0.180	-4.090	<0.001	-1.089	-0.384
5 or more	-1.259	0.179	-7.040	<0.001	-1.609	-0.909

Table 74: Income ≥ \$75,000 DCE Treatment Attributes With TTO, 5 yr. Durability

<i>Income ≥ \$75,000</i>	Coef.	Std. Err.	z	P> z	95% Conf.Interval	
<i>Treatment Administration</i>						
One-time IV infusion, 5 years * years	(reference)					
One-time IV infusion, 10 years * years	0.020	0.016	1.250	0.210	-0.011	0.052
1-2 times SQ injection per month * years	-0.017	0.015	-1.160	0.248	-0.046	0.012
2-3 times IV infusion per week * years	-0.041	0.015	-2.660	0.008	-0.071	-0.011
<i>Mental health</i>						
No concern about your hemophilia * years	(reference)					
Occasionally concerned about your hemophilia * years	0.002	0.014	0.140	0.891	-0.025	0.029
Always concerned about your hemophilia * years	-0.044	0.011	-3.910	<0.001	-0.066	-0.022
<i>Chronic pain</i>						
No * years	(reference)					
Yes * years	-0.003	0.009	-0.330	0.739	-0.022	0.015
<i>Bleeding</i>						
None * years	(reference)					
1 - 4 times * years	-0.047	0.013	-3.740	<0.001	-0.072	-0.023
5 or more * years	-0.071	0.014	-4.970	<0.001	-0.099	-0.043
<i>Life Duration</i>	0.068	0.029	2.370	0.018	0.012	0.124

Table 75: Income ≥ \$75,000 DCE Treatment Attributes With TTO, 10 yr. Durability

<i>Income ≥ \$75,000</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 10 years * years	ref					
One-time IV infusion, 5 years * years	-0.020	0.016	-1.250	0.210	-0.052	0.011
1-2 times SQ injection per month * years	-0.038	0.017	-2.210	0.027	-0.071	-0.004
2-3 times IV infusion per week * years	-0.061	0.016	-3.770	<0.001	-0.093	-0.029
<i>Mental health</i>						
No concern about your hemophilia * years	(reference)					
Occasionally concerned about your hemophilia * years	0.002	0.014	0.140	0.891	-0.025	0.029
Always concerned about your hemophilia * years	-0.044	0.011	-3.910	<0.001	-0.066	-0.022
<i>Chronic pain</i>						
No * years	(reference)					
Yes * years	-0.003	0.009	-0.330	0.739	-0.022	0.015
<i>Bleeding</i>						
None * years	(reference)					
1 - 4 times * years	-0.047	0.013	-3.740	<0.001	-0.072	-0.023
5 or more * years	-0.071	0.014	-4.970	<0.001	-0.099	-0.043
<i>Life duration</i>	0.088	0.028	3.110	0.002	0.033	0.144

Table 76: Income ≥ \$75,000 Annualized Disutility Decrement 5 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 5 years * years	(reference)			
One-time IV infusion, 10 years * years	0.020	0.300	0.015	0.210
1-2 times SQ injection per month * years	-0.017	-0.253	-0.013	0.248
2-3 times IV infusion per week * years	-0.041	-0.598	-0.030	0.008
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally concerned about your hemophilia * years	0.002	0.028	0.001	0.891
Always concerned about your hemophilia * years	-0.044	-0.649	-0.032	<0.001
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	-0.003	-0.046	-0.002	0.739
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.047	-0.695	-0.035	<0.001
5 or more * years	-0.071	-1.041	-0.052	<0.001

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 77: Income ≥ \$75,000 Annualized Disutility Decrement 10 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 10 years * years	(reference)			
One-time IV infusion, 5 years * years	-0.020	-0.232	-0.012	0.210
1-2 times SQ injection per month * years	-0.038	-0.427	-0.021	0.027
2-3 times IV infusion per week * years	-0.061	-0.694	-0.035	<0.001
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally concerned about your hemophilia * years	0.002	0.022	0.001	0.891
Always concerned about your hemophilia * years	-0.044	-0.501	-0.025	<0.001
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	-0.003	-0.036	-0.002	0.739
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.047	-0.537	-0.027	<0.001
5 or more * years	-0.071	-0.804	-0.040	<0.001

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 78: Income \$25,000-\$49,999 DCE Treatment Attributes Without TTO, 5 yr. Durability

<i>Income \$25000-\$49000</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment Administration</i>						
One-time IV infusion, 5 years	(reference)					
One-time IV infusion, 10 years	0.576	0.254	2.270	0.023	0.078	1.073
1-2 times SQ injection per month	-0.968	0.288	-3.370	0.001	-1.532	-0.405
2-3 times IV infusion per week	-2.346	0.319	-7.360	<0.001	-2.971	-1.722
<i>Mental Health</i>						
none	(reference)					
Occasionally concerned about your hemophilia	-0.457	0.252	-1.820	0.069	-0.950	0.036
Always concerned about your hemophilia	-1.612	0.262	-6.150	<0.001	-2.127	-1.098
<i>Chronic Pain</i>						
None	(reference)					
Chronic Pain-Yes	-0.532	0.175	-3.050	0.002	-0.875	-0.190
<i>Bleeding</i>						
none	(reference)					
1-4 times	-0.464	0.239	-1.940	0.052	-0.933	0.004
5 or more	-0.466	0.225	-2.080	0.038	-0.906	-0.026

Table 79: Income \$25,000-\$49,999 DCE Treatment Attributes Without TTO, 10 yr. Durability

<i>Income \$25000-\$49000</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment administration</i>						
One-time IV infusion, 10 years	(reference)					
One-time IV infusion, 5years	-0.576	0.254	-2.270	0.023	-1.073	-0.078
1-2 times SQ injection per month	-1.544	0.311	-4.960	<0.001	-2.154	-0.934
2-3 times IV infusion per week	-2.922	0.343	-8.530	<0.001	-3.593	-2.250
<i>Mental health</i>						
none	(reference)					
Occasionally concerned about your hemophilia	-0.457	0.252	-1.820	0.069	-0.950	0.036
Always concerned about your hemophilia	-1.612	0.262	-6.150	<0.001	-2.127	-1.098
<i>Chronic pain</i>						
none	(reference)					
yes	-0.532	0.175	-3.050	0.002	-0.875	-0.190
<i>Bleeding</i>						
none						
1-4 times	-0.464	0.239	-1.940	0.052	-0.933	0.004
5 or more	-0.466	0.225	-2.080	0.038	-0.906	-0.026

Table 80: Income \$25,000-\$49,999 DCE Treatment Attributes With TTO, 5 yr. Durability

<i>Income \$25000-\$49000</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 5 years *	(reference)					
years						
One-time IV infusion, 10 years *						
years	0.029	0.019	1.520	0.129	-0.009	0.067
1-2 times SQ injection per month *						
years	-0.027	0.018	-1.500	0.135	-0.062	0.008
2-3 times IV infusion per week *						
years	-0.085	0.019	-4.500	<0.001	-0.122	-0.048
<i>Mental health</i>						
No concern about your hemophilia	(reference)					
* years						
Occasionally concerned about your						
hemophilia * years	0.007	0.017	0.430	0.669	-0.026	0.040
Always concerned about your						
hemophilia * years	-0.053	0.014	-3.730	<0.001	-0.081	-0.025
<i>Chronic pain</i>						
No * years	(reference)					
Yes * years	0.004	0.012	0.370	0.714	-0.018	0.027
<i>Bleeding</i>						
None * years	(reference)					
1 - 4 times * years	-0.053	0.016	-3.390	0.001	-0.083	-0.022
5 or more * years	-0.059	0.017	-3.420	0.001	-0.092	-0.025
<i>Life duration</i>	0.103	0.035	2.950	0.003	0.034	0.172

Table 81: Income \$25,000-\$49,999 DCE Treatment Attributes With TTO, 10 yr. Durability

<i>Income \$25000-\$49000</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 10 years *	(reference)					
years						
One-time IV infusion, 5 years *						
years	-0.029	0.019	-1.520	0.129	-0.067	0.009
1-2 times SQ injection per month *						
years	-0.056	0.021	-2.730	0.006	-0.097	-0.016
2-3 times IV infusion per week *						
years	-0.115	0.021	-5.550	<0.001	-0.155	-0.074
<i>Mental health</i>						
No concern about your hemophilia	(reference)					
* years						
Occasionally concerned about your						
hemophilia * years	0.007	0.017	0.430	0.669	-0.026	0.040
Always concerned about your						
hemophilia * years	-0.053	0.014	-3.730	<0.001	-0.081	-0.025
<i>Chronic pain</i>						
No * years	(reference)					
Yes * years	0.004	0.012	0.370	0.714	-0.018	0.027
<i>Bleeding</i>						
None * years	(reference)					
1 - 4 times * years	-0.053	0.016	-3.390	0.001	-0.083	-0.022
5 or more * years	-0.059	0.017	-3.420	0.001	-0.092	-0.025
<i>Life duration</i>	0.133	0.034	3.860	<0.001	0.065	0.200

Table 82: Income \$25,000-\$49,999 Annualized Disutility Decrement 5 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 5 years * years	(reference)			
One-time IV infusion, 10 years * years	0.029	0.286	0.014	0.129
1-2 times SQ injection per month * years	-0.027	-0.259	-0.013	0.135
2-3 times IV infusion per week * years	-0.085	-0.825	-0.041	<0.001
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally concerned about your hemophilia * years	0.007	0.070	0.003	0.669
Always concerned about your hemophilia * years	-0.053	-0.513	-0.026	<0.001
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	0.004	0.041	0.002	0.714
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.053	-0.512	-0.026	0.001
5 or more * years	-0.059	-0.570	-0.029	0.001

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 83: Income \$25,000-\$49,999 Annualized Disutility Decrement 10 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 10 years *	(reference)			
years				
One-time IV infusion, 5 years * years	-0.029	-0.222	-0.011	0.129
1-2 times SQ injection per month *				
years	-0.056	-0.424	-0.021	0.006
2-3 times IV infusion per week *				
years	-0.115	-0.864	-0.043	<0.001
<i>Mental health</i>				
No concern about your hemophilia *	(reference)			
years				
Occasionally concerned about your hemophilia * years	0.007	0.054	0.003	0.669
Always concerned about your hemophilia * years	-0.053	-0.399	-0.020	<0.001
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	0.004	0.032	0.002	0.714
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.053	-0.398	-0.020	0.001
5 or more * years	-0.059	-0.443	-0.022	0.001

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 84: Income \$50,000-\$74,999 DCE Treatment Attributes Without TTO, 5 yr.**Durability**

<i>Income \$50,000-\$74,999</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 5 years	(reference)					
One-time IV infusion, 10 years	0.659	0.135	4.890	<0.001	0.395	0.923
1-2 times SQ injection per month	-1.840	0.199	-9.260	<0.001	-2.230	-1.450
2-3 times IV infusion per week	-2.303	0.184	-12.510	<0.001	-2.664	-1.942
<i>Mental health</i>						
No concern about your hemophilia	(reference)					
Occasionally concerned about your hemophilia	-0.196	0.135	-1.440	0.149	-0.461	0.070
Always concerned about your hemophilia	-2.348	0.171	-13.760	<0.001	-2.682	-2.013
<i>Chronic pain</i>						
No	(reference)					
Yes	-0.140	0.087	-1.610	0.107	-0.310	0.030
<i>Bleeding</i>						
None	(reference)					
1 - 4 times	-0.274	0.128	-2.140	0.032	-0.525	-0.024
5 or more	-0.392	0.120	-3.280	0.001	-0.627	-0.158

Table 85: Income \$50,000-\$74,999 DCE Treatment Attributes Without TTO, 10 yr.**Durability**

<i>Income \$50,000-\$74,999</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 10 years	(reference)					
One-time IV infusion, 5 years	-0.659	0.135	-4.890	<0.001	-0.923	-0.395
1-2 times SQ injection per month	-2.499	0.196	-12.760	<0.001	-2.883	-2.115
2-3 times IV infusion per week	-2.962	0.189	-15.710	<0.001	-3.331	-2.592
<i>Mental health</i>						
No concern about your hemophilia	(reference)					
Occasionally concerned about your hemophilia	-0.196	0.135	-1.440	0.149	-0.461	0.070
Always concerned about your hemophilia	-2.348	0.171	-13.760	<0.001	-2.682	-2.013
<i>Chronic pain</i>						
No	(reference)					
Yes	-0.140	0.087	-1.610	0.107	-0.310	0.030
<i>Bleeding</i>						
None	(reference)					
1 - 4 times	-0.274	0.128	-2.140	0.032	-0.525	-0.024
5 or more	-0.392	0.120	-3.280	0.001	-0.627	-0.158

Table 86: Income \$50,000-\$74,999 DCE Treatment Attributes With TTO, 5 yr. Durability

<i>Income \$50,000-\$74,999</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment Administration</i>						
One-time IV infusion, 5 years * years	(reference)					
One-time IV infusion, 10 years * years	0.064	0.011	5.880	<0.001	0.043	0.086
1-2 times SQ injection per month * years	-0.099	0.012	-8.420	<0.001	-0.122	-0.076
2-3 times IV infusion per week * years	-0.117	0.012	-10.100	<0.001	-0.140	-0.094
<i>Mental health</i>						
No concern about your hemophilia * years	(reference)					
Occasionally concerned about your hemophilia * years	0.010	0.010	1.050	0.295	-0.009	0.029
Always concerned about your hemophilia * years	-0.114	0.010	-11.960	<0.001	-0.133	-0.095
<i>Chronic pain</i>						
No * years	(reference)					
Yes * years	0.011	0.007	1.610	0.107	-0.002	0.025
<i>Bleeding</i>						
None * years	(reference)					
1 - 4 times * years	-0.021	0.009	-2.310	0.021	-0.038	-0.003
5 or more * years	-0.046	0.010	-4.750	<0.001	-0.065	-0.027
<i>Life duration</i>	0.109	0.022	4.950	<0.001	0.066	0.152

Table 87: Income \$50,000-\$74,999 DCE Treatment Attributes With TTO, 10 yr. Durability

<i>Income \$50,000-\$74,999</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 10 years * years	(reference)					
One-time IV infusion, 5 years * years	-0.064	0.011	-5.880	<0.001	-0.086	-0.043
1-2 times SQ injection per month * years	-0.163	0.013	-12.510	<0.001	-0.189	-0.137
2-3 times IV infusion per week * years	-0.181	0.013	-14.220	<0.001	-0.206	-0.156
<i>Mental health</i>						
No concern about your hemophilia * years	(reference)					
Occasionally concerned about your hemophilia * years	0.010	0.010	1.050	0.295	-0.009	0.029
Always concerned about your hemophilia * years	-0.114	0.010	-11.960	<0.001	-0.133	-0.095
<i>Chronic pain</i>						
No * years	(reference)					
Yes * years	0.011	0.007	1.610	0.107	-0.002	0.025
<i>Bleeding</i>						
None * years	(reference)					
1 - 4 times * years	-0.021	0.009	-2.310	0.021	-0.038	-0.003
5 or more * years	-0.046	0.010	-4.750	<0.001	-0.065	-0.027
<i>Life duration</i>	0.173	0.021	8.190	<0.001	0.132	0.215

Table 88: Income \$50,000-\$74,999 Annualized Disutility Decrement 5 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 5 years * years	(reference)			
One-time IV infusion, 10 years * years	0.064	0.591	0.030	<0.001
1-2 times SQ injection per month * years	-0.099	-0.907	-0.045	<0.001
2-3 times IV infusion per week * years	-0.117	-1.076	-0.054	<0.001
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally concerned about your hemophilia * years	0.010	0.094	0.005	0.295
Always concerned about your hemophilia * years	-0.114	-1.048	-0.052	<0.001
<i>Chronic pain</i>				
No * years	(reference)			0.107
Yes * years	0.011	0.104	0.005	
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.021	-0.190	-0.009	0.021
5 or more * years	-0.046	-0.420	-0.021	<0.001

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 89: Income \$50,000-\$74,999 Annualized Disutility Decrement 10 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 10 years * years	(reference)			
One-time IV infusion, 5 years * years	-0.064	-0.371	-0.019	<0.001
1-2 times SQ injection per month * years	-0.163	-0.941	-0.047	<0.001
2-3 times IV infusion per week * years	-0.181	-1.048	-0.052	<0.001
<i>Mental health</i>				
No concern about your hemophilia * years	(reference)			
Occasionally concerned about your hemophilia * years	0.010	0.059	0.003	0.295
Always concerned about your hemophilia * years	-0.114	-0.659	-0.033	<0.001
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	0.011	0.066	0.003	0.107
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.021	-0.119	-0.006	0.021
5 or more * years	-0.046	-0.264	-0.013	<0.001

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 90: Income < \$25,000 DCE Treatment Attributes Without TTO, 5 yr. Durability

<i>Income Less \$25000</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment Administration</i>						
One-time IV infusion, 5 years	(reference)					
One-time IV infusion, 10 years	-0.015	0.403	-0.040	0.970	-0.805	0.775
1-2 times SQ injection per month	-0.541	0.381	-1.420	0.156	-1.289	0.206
2-3 times IV infusion per week	-1.354	0.423	-3.200	0.001	-2.183	-0.525
<i>Mental health</i>						
none	(reference)					
Occasionally concerned about your hemophilia	0.227	0.354	0.640	0.521	-0.467	0.922
Always concerned about your hemophilia	-0.318	0.294	-1.080	0.280	-0.894	0.259
<i>Chronic pain</i>						
None	(reference)					
Chronic Pain-Yes	-0.427	0.238	-1.790	0.073	-0.893	0.040
<i>Bleeding</i>						
none						
1-4 times	-0.198	0.309	-0.640	0.523	-0.804	0.408
5 or more	-1.489	0.348	-4.280	<0.001	-2.171	-0.807

Table 91: Income <\$25,000 DCE Treatment Attributes Without TTO, 10 yr. Durability

<i>Income Less \$25000</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment administration</i>						
One-time IV infusion, 10 years	(reference)					
One-time IV infusion, 5years	0.015	0.403	0.040	0.970	-0.775	0.805
1-2 times SQ injection per month	-0.526	0.409	-1.280	0.199	-1.328	0.277
2-3 times IV infusion per week	-1.339	0.400	-3.350	0.001	-2.123	-0.555
<i>Mental health</i>						
none	(reference)					
Occasionally concerned about your hemophilia	0.227	0.354	0.640	0.521	-0.467	0.922
Always concerned about your hemophilia	-0.318	0.294	-1.080	0.280	-0.894	0.259
<i>Chronic pain</i>						
none	(reference)					
yes	-0.427	0.238	-1.790	0.073	-0.893	0.040
<i>Bleeding</i>						
none	(reference)					
1-4 times	-0.198	0.309	-0.640	0.523	-0.804	0.408
5 or more	-1.489	0.348	-4.280	<0.001	-2.171	-0.807

Table 92: Income <\$25,000 DCE Treatment Attributes With TTO, 5 yr. Durability

<i>Income Less \$25000</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 5 years * years	(reference)					
One-time IV infusion, 10 years * years	0.008	0.031	0.270	0.786	-0.052	0.069
1-2 times SQ injection per month * years	0.004	0.027	0.160	0.873	-0.048	0.056
2-3 times IV infusion per week * years	-0.011	0.028	-0.390	0.695	-0.067	0.044
<i>Mental health</i>						
No concern about your hemophilia * years	(reference)					
Occasionally concerned about your hemophilia * years	0.020	0.026	0.760	0.444	-0.031	0.072
Always concerned about your hemophilia * years	0.002	0.021	0.080	0.937	-0.039	0.042
<i>Chronic pain</i>						
No * years	(reference)					
Yes * years	-0.004	0.017	-0.250	0.805	-0.038	0.030
<i>Bleeding</i>						
None * years	(reference)					
1 - 4 times * years	-0.047	0.023	-2.020	0.044	-0.093	-0.001
5 or more * years	-0.054	0.026	-2.030	0.042	-0.105	-0.002
<i>Life duration</i>	0.028	0.053	0.520	0.603	-0.077	0.133

Table 93: Income <\$25,000 DCE Treatment Attributes With TTO, 10 yr. Durability

<i>Income Less \$25000</i>	<i>Coef.</i>	<i>Std. Err.</i>	<i>z</i>	<i>P> z </i>	<i>95% Conf.Interval</i>	
<i>Treatment</i>						
One-time IV infusion, 10 years *	(reference)					
years						
One-time IV infusion, 5 years * years	-0.008	0.031	-0.270	0.786	-0.069	0.052
1-2 times SQ injection per month *						
years	-0.004	0.031	-0.130	0.896	-0.066	0.057
2-3 times IV infusion per week *						
years	-0.019	0.030	-0.650	0.516	-0.078	0.039
<i>Mental health</i>						
No concern about your hemophilia *	(reference)					
years						
Occasionally concerned about your						
hemophilia * years	0.020	0.026	0.760	0.444	-0.031	0.072
Always concerned about your						
hemophilia * years	0.002	0.021	0.080	0.937	-0.039	0.042
<i>Chronic pain</i>						
No * years	(reference)					
Yes * years	-0.004	0.017	-0.250	0.805	-0.038	0.030
<i>Bleeding</i>						
None * years	(reference)					
1 - 4 times * years	-0.047	0.023	-2.020	0.044	-0.093	-0.001
5 or more * years	-0.054	0.026	-2.030	0.042	-0.105	-0.002
<i>Life duration</i>	0.036	0.052	0.690	0.488	-0.066	0.138

Table 94: Income <\$25,000 Annualized Disutility Decrement 5 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 10 years *	(reference)			
One-time IV infusion, 5 years * years	0.008	0.301	0.015	0.786
1-2 times SQ injection per month *				
years	0.004	0.153	0.008	0.873
2-3 times IV infusion per week *				
years	-0.011	-0.401	-0.020	0.695
<i>Mental health</i>				
No concern about your hemophilia *	(reference)			
years				
Occasionally concerned about your hemophilia * years	0.020	0.724	0.036	0.444
Always concerned about your hemophilia * years	0.002	0.059	0.003	0.937
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	-0.004	-0.155	-0.008	0.805
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.047	-1.694	-0.085	0.044
5 or more * years	-0.054	-1.930	-0.096	0.042

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

Table 95: Income <\$25,000 Annualized Disutility Decrement 10 Yr. Reference

<i>Variable</i>	<i>Coefficient</i>	<i>Disutility*</i>	<i>Annualized disutility (20 TTO years)</i>	<i>p-value</i>
<i>Treatment</i>				
One-time IV infusion, 10 years *	(reference)			
years				
One-time IV infusion, 5 years * years	-0.008	-0.231	-0.012	0.786
1-2 times SQ injection per month *				
years	-0.004	-0.113	-0.006	0.516
2-3 times IV infusion per week *				
years	-0.019	-0.540	-0.027	0.896
<i>Mental health</i>				
No concern about your hemophilia *	(reference)			
years				
Occasionally concerned about your hemophilia * years	0.020	0.557	0.028	0.444
Always concerned about your hemophilia * years	0.002	0.045	0.002	0.937
<i>Chronic pain</i>				
No * years	(reference)			
Yes * years	-0.004	-0.119	-0.006	0.805
<i>Bleeding</i>				
None * years	(reference)			
1 - 4 times * years	-0.047	-1.302	-0.065	0.044
5 or more * years	-0.054	-1.483	-0.074	0.042

Disutility*=coefficient for treatment attribute/coefficient for life duration attribute

Annualized disutility (20 TTO years)=coefficient for treatment attribute/ (coefficient for life duration attribute *20)

APPENDIX

Appendix A: Pilot Questionnaire

Patient Preferences for Treatment of Hemophilia A

Pilot Pre-Test Survey

You are invited to participate in the design of a research study that will measure preferences for different hemophilia A treatments. The study is a discrete choice experiment (DCE), **using Time Trade Off (TTO) Methodology** in which subjects will complete a questionnaire that will ask them to choose between different hypothetical scenarios. Using the answers to the questionnaire, we will determine what is most important to patients and caregivers in hemophilia A treatment. This will inform future hemophilia A treatment decisions.

You are being asked to participate in the design of this study because you are a patient with hemophilia A. For this pilot pre-testing, we would like you to help us determine 1) whether the questions and answers listed below are written clearly and understandably, 2) whether the questions and answers listed below are relevant to your hemophilia A treatment (and which are the most and the least relevant), and 3) whether the answer options are normal or typical in your treatment experience. We thank you for your participation.

The next few questions are meant to evaluate your thoughts on your hemophilia, including treatment, safety, how treatment is administered, your quality of life, and time trade off.

1. How many times in one year do you bleed?
 - None
 - 1-2
 - 3-4
 - ≥ 5

2. What level of risk of inhibitor development are you comfortable with?
 - High
 - Medium
 - Low

3. What level of risk of thrombotic (clot) events are you comfortable with?
 - High
 - Medium
 - Low

4. How often would you prefer to receive routine treatment with the drug?
 - None

- A few times a week (i.e., every other day, 3 times a week, 2 times a week)
 - Once a week
 - Once every 2 weeks
5. How would you prefer to receive to receive your treatment?
- IV infusion (peripheral vein)
 - Port infusion/central line
 - Subcutaneous injection (under-the-skin)
 - Gene Therapy
6. To what degree would you prefer to be in order to perform your normal activities without fear of bleeding?
- High
 - Low

The research coordinator will now ask you questions, based on what type of treatment you would prefer, if it helped you live longer. Please keep in mind, these are all hypothetical situations, that will give the research team, a better understanding of treatment preferences. For example, are you willing to get gene therapy, live for 10 years with no treatment, then die? Or receive treatment a few times a week, live for 15 years, then die?

PLEASE NOTE! For each of the questions above, based on the responses and your comments after speaking with the research coordinator, the questions will be developed further, to include time **trade-off questions**, such as the example below, when you will pick a treatment scenario.

Attribute	Treatment A	Treatment B
Annual bleeding rate	3-4	None
Risk of inhibitor development	High	High
Risk of thrombotic (clot) events or other treatment side effects	High risk	High risk
Frequency of treatment administration	Once a week	None
Live for # of years, then die (TIME TRADE OFF)	10 year	15 years

Appendix B: Attributes and Levels for DCE_{TTO}

<u>Category</u>	<u>Attribute</u>	<u>Levels</u>
Treatment	Frequency and mode of treatment administration	One-time IV infusion that works for 5 years, followed by your regular hemophilia treatment
		One-time IV infusion that works for 10 years, followed by your regular hemophilia treatment
		2-3 times IV infusion per week
		1-2 times SQ injection per month
Mental health	Ability to perform normal activities	Always concerned about your hemophilia.
		Occasionally concerned about your hemophilia.
		No concern about your hemophilia.
Chronic pain	Pain from a persistent cause	Yes
		No
Bleeding	Number of Bleeds Per Year	None
		1 - 4
		5 or more
Life Duration	Remaining Years of Life	10 years
		15 years
		20 years

Appendix C: Example of DCE_{TTO} Choice Set (Which scenario is better?)

<u>Attribute</u>	<u>Treatment A</u>	<u>Treatment B</u>
Frequency and mode of administration	2-3 times a week IV infusion	One-time IV infusion that works for 5 years, followed by your regular hemophilia treatment
Ability to perform normal activities	Always concerned about your hemophilia.	No concern about your hemophilia.
Pain from a persistent cause	Yes	No
Number of Bleeds Per Year	1-4	None
Remaining years of life	10 years	20 years

Appendix D: Patient Characteristics/Demographics

Patient Characteristics/Demographics

Last Name, First Name

Date of Birth

Gender (Male/Female/Non-binary)

Race

White
Black or African American,
Native Hawaiian or Pacific Islander
Native Indian or Alaska Native
Other
Prefer Not to Answer

Ethnicity

Hispanic
Non-Hispanic

Marital status

Single
Married
Separated/divorced/widowed
Prefer Not to Answer

Employment (Select all that apply)

Working full-time
Working part-time
On-long-term sick/ disability
Unemployed
Retired
Student full-time
Student part-time
Other
Prefer not to answer

Annual income level

< \$25 000
\$25 000–\$49,999
\$50,000–\$74,999
≥ \$ 75,000
Don't know/prefer not to answer

Health Insurance

Commercial or Private
Medicaid
Medicare
None
Other

Education level

High-school diploma or equivalent (e.g., GED)
Some college or 2-year degree (e.g., Associates, Vocational, Technical)
4-year college degree (e.g., Bachelors)
More than 4-year degree (e.g., Masters, PhD, MD, etc.)
Prefer not to answer

Disease severity

Patient Characteristics/Demographics

Mild
Moderate
Severe

Annual bleed rate

0
1–4 bleeds
≥ 5 bleeds
Don't Know

FVIII inhibitors in the past

Yes
No

Current treatment

On demand
Prophylaxis
Other
None
Don't Know

Type of treatment

Bypassing concentrates
Short-acting FVIII
Long-acting FVIII
Non-factor products (e.g., emicizumab)
Other products (e.g., stimate)
None

Frequency of treatment

More than once a week (2,3,4 times a week)
Once every week
Once every 2 weeks
Once every 4 weeks
Less often than 4 weeks (once every 5 or 6 weeks)
Don't know

Previous/current use of central device

Yes
No
Don't Know

Previous/current joint problems

Yes
No

Previous/current joint procedure

Yes
No

HIV

Yes
No

History of hepatitis C

Yes
No

General health over the past 4 weeks

Excellent
Very good
Good
Fair
Poor

Appendix E: EQ-5D-5L

Under each heading, please check the ONE box that best describes your health TODAY.

MOBILITY

- I have no problems walking ☐
- I have slight problems walking ☐
- I have moderate problems walking ☐
- I have severe problems walking ☐
- I am unable to walk ☐

SELF-CARE

- I have no problems washing or dressing myself ☐
- I have slight problems washing or dressing myself ☐
- I have moderate problems washing or dressing myself ☐
- I have severe problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

- I have no problems doing my usual activities ☐
- I have slight problems doing my usual activities ☐
- I have moderate problems doing my usual activities ☐
- I have severe problems doing my usual activities ☐
- I am unable to do my usual activities ☐

PAIN / DISCOMFORT

- I have no pain or discomfort ☐
- I have slight pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have severe pain or discomfort ☐
- I have extreme pain or discomfort ☐

ANXIETY / DEPRESSION

- I am not anxious or depressed ☐
- I am slightly anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am severely anxious or depressed ☐
- I am extremely anxious or depressed ☐

Visual Analogue Scale

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY =

