STATISTICAL ANALYSIS PLAN (SAP)

FOR NON-INTERVENTIONAL STUDIES

[redacted]

NON-INTERVENTIONAL STUDY PROTOCOL

<B1821056>

UNDERSTANDING HEMOPHILIA A AND B ADMINISTRATION PATTERNS

STATISTICAL ANALYSIS PLAN
(SAP)

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TABLE OF CONTENTS

LIST OF TABLES

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1. AMENDMENTS FROM PREVIOUS VERSION(S)

None.

2. INTRODUCTION

Hemophilia A and B are chronic inherited bleedings disorders caused by an X-chromosome linked deficiency in coagulation factors.[1] Although the incidence of hemophilia is relatively low, it imposes a high level of burden to sufferers, caregivers, and society. As hemophilia requires lifetime treatment it is associated with substantial costs, particularly direct costs. Factor replacement therapy, used for both prophylaxis and on-demand therapy, is the mainstay of hemophilia treatment and has been estimated to cost more than $250,000 per adult in the United States. Depending on the disease severity and treatment regimen, factor replacement products accounts for 45% to 93% of the total medical costs for hemophilia.[2]

Newer, longer acting treatments for hemophilia have recently been approved by the FDA. Alprolix is a longer-acting treatment than traditional treatments that was approved by the FDA in March, 2014 for hemophilia B. And similarly, for hemophilia A, Eloctate was approved in 2014 and Adynovate in 2015. These newer, longer-acting drugs require less frequent administrations than Pfizer's BeneFIX (for hemophilia B) and Xyntha (for hemophilia A). Even a relatively small change in frequency of administration has the potential to translate into 50 or fewer infusions per year and a correspondingly smaller number of units infused per patient. The expected advantages of fewer infusions from longer acting products include greater patient compliance, less disruptions in daily activities and less reliance on others to help with infusions.[1] However; these benefits are only realized if there is indeed fewer infusions associated with the longer-acting products compared with the shorter-acting products. To date, little is known about real world administration patterns for longer-acting treatments in comparison to traditional treatments. Pfizer is seeking to generate evidence which validates the hypothesis they have that Alprolix , Eloctate, and Adynovate are being dosed more often than their labeling indicates, thus potentially costing payors and patients more money compared to traditional treatments, like BeneFIX and Xyntha.

2.1. Study Design

This study will be conducted as a prospective observational, cross-sectional epidemiological study in U.S. site-based clinical practice settings. Participating physicians / clinicians at approximately 30 sites will enroll approximately 300 patients for inclusion in the study. Participating patients – or their caregiver in the case of patients under the age of 18 - will be consented to participate. After this consent occurs, the physicians will complete a retrospective chart review on each enrolled patient, entering their findings into a chart review form (CRF) online. Patients will complete a one-time study questionnaire, which should take approximately 20 minutes to complete, by accessing a link online. The patient questionnaire will include self-report questions regarding patient demographics, clinical profile, treatment, and physician-patient relationship, along with several validated scales to assess health-related quality of life. In addition, patients will submit their health insurance claims data to the study team for analysis. All survey questionnaires will be in English. All respondents will be provided remuneration for their participation.

2.2. Study population

The study will involve approximately 300 patients recruited from approximately 30 participating sites. The table below shows the specific breakdown in sample size for each hemophilia type and treatment cohort.

Table 1. Study Sample

	Sample Size	
	Xyntha	**Eloctate or Adynovate**
Hem A Patients / Caregivers of Hem A Patients	75	75
Total Hem A	150	
	Alprolix	**BeneFIX**
Hem B Patients / Caregivers of Hem B Patients	75	75
Total Hem B	150	
TOTAL	300	

This study will compare Xyntha vs. Eloctate /Adynovate among hemophilia A patients and Alprolix vs. BeneFIX among hemophilia B patients. For a mean difference comparing two independent means with the anticipated sample sizes (75 vs. 75; 150 total) with α=0.05, two-sided, 80% power, the expected minimal detectable effect (MDE) would be Cohen's d=0.46. This study with the anticipated sample size is powered to detect at least a moderate effect size.

The inclusion and exclusion criteria for physicians and patients are specified below.

Physician/Clinician Participants Inclusion Criteria

Participating sites must undergo a contracting procedure and agree to follow the study protocol as well as all terms of the study contract. Participating sites will be led by a physician / clinician (eg, nurse, nurse practitioner, physician assistant, etc.) who will serve as that site's PI/sub-PI. The participating PI/sub-PI must meet all the following inclusion criteria to participate in the study:

- Must be a healthcare provider with at least 60% of time spent in direct patient care
- Board-certified or eligible with a Specialty in Hematology or Hematology-Oncology (if hematologist-oncologist, at least 10% practice is dedicated to treatment of hemophilia)
- Currently manages at least 10 hemophilia A and/or B patients
- Must not be on the FDA debarment list

Patient Participants Inclusion Criteria

Participants must meet all of the following inclusion criteria to be eligible for inclusion in the study:

- Willing and able to provide informed consent
- Diagnosed with hemophilia A or B
- Current disease severity is either moderately severe or severe with a clotting factor level of ≤5%
- If suffering from hemophilia A, must be currently taking Xyntha (or another standard half-life treatment), Adynovate or Eloctate for at least six months.
    - If currently taking Adynovate or Eloctate, must have been switched from a standard half-life treatment and had been on that prior treatment for at least six months.
- If suffering from hemophilia B, must be currently taking BeneFIX or Alprolix for at least six months.
    - If currently taking Alprolix, must have switched from BeneFIX and had been on that prior treatment for at least six months.
- Infuse at least 3 times per month

In the event of a caregiver responding on behalf of the patient, the above inclusion criteria will be applied for the patient for whom the caregiver is responding.

Patient Participants Exclusion Criteria

Currently enrolled in a clinical trial and/or using investigational product for the treatment of his or her hemophilia

2.3. Study Objectives

The study's primary objective is to compare the dosing and resource utilization patterns of standard half-life treatments vs. extended half-life treatments for the management of hemophilia A and B

- Specifically, the dosing and resource utilization patterns of Xyntha (or other standard half-life treatments) vs. Adynovate or Eloctate (extended half-life) will be assessed for treatment of hemophilia A
- And similarly, the dosing and resource utilization patterns of BeneFIX (standard half-life) vs. Alprolix (extended half-life) will be assessed for treatment of hemophilia B

3. ANALYSIS SETS/ POPULATIONS

3.1. Full analysis set

All physicians (N=30) and hemophilia A (N=150) and B (N=150) patients from the study will be available for analysis.

3.2. Subgroups

Subgroups will include the different treatment cohorts as defined above under "Treatment/cohort levels" and outlined again below.

- Patients on Xyntha (or other standard half-life treatments) vs. Adynovate or Eloctate (extended half-life treatments) for treatment of hemophilia A
- Patients on BeneFIX (standard half-life treatment) vs. Alprolix (extended half-life treatment) for treatment of hemophilia B

4. ENDPOINTS AND COVARIATES

4.1. Efficacy/ Effectiveness Endpoint(s)

Physician Participants:

Physician/Practice Characteristics

- Primary medical specialty
- Board certification
- Percentage of time spent in direct patient care
- Percentage of their practice dedicated to the treatment of hemophilia
- Number of moderate to severe hemophilia A and B patients currently managed
- Number of hemophilia A and B patients currently participating in clinical trials
- Insurance plans accepted

Patient Treatment Pattern (from patient chart)

- Current and previous hemophilia treatment
- Reasons for discontinuation
- Duration of treatment used
- Whether prescription was prophylaxis or on-demand
- Number of infusions per month prescribed

- Frequency of doctor visits for management of hemophilia

Patient Demographics (from patient chart)

- Age
- Sex
- Race
- Weight
- Height
- Health insurance type

Patient Clinical Profile (from patient chart)

- Age of diagnosis
- Primary symptoms
- Disease severity
- Joint health score
- Comorbidities

Patient Participants (self-reported or caregiver reported):

Patient Demographics

- Sex
- Age
- Race/ethnicity
- Marital status
- Household income
- Education*
- Employment status*
- Health insurance type

- Healthcare insurer
- Pharmacy insurer

*In the case of caregivers responding, caregiver's education and employment will also be collected.

Patient Clinical Profile

- Disease severity
- Clotting factor level

Patient Treatment

- When are infusions done
- Number of infusions in a typical month
- Previous and current hemophilia treatments
- Duration of previous and current hemophilia treatments used
- Recent factor use behavior
- Whether participated in clinical trials within the past 12 months

Physician Patient Relationship

- Patient's relationship with his/her physician in regards treatment decisions for hemophilia rated as either paternalistic, informative, interpretive, or deliberate depending upon which relationship description the patient selects.

Validated Scales for Health-Related Quality of Life

Global health-related quality of life scales

36 Item Short Form Health Survey (SF-36; adult)[3]: The SF-36v2 is a multipurpose, generic health status instrument comprised of 36 questions. These items map onto eight health domains: physical functioning, physical role limitations, bodily pain, general health, vitality, social functioning, emotional role limitations, and mental health. In addition to these eight health domains, there are two component summary scores: the physical component summary (PCS) and the mental component summary (MCS).

10 Item Short Health Survey (SF-10; caregiver reported for child)[4]**:** A-parent completed survey that contains 10 questions adapted from the Child Health Questionnaire (CHQ). The SF-10 assesses a wide range of domains and is scored to produce a physical and psychosocial health summary score. This survey is intended for children aged 5 through 18.

Hemophilia-specific health-related quality of life scales

Hemophilia-Specific Quality of Life Index for Adults (HAEM-A-QOL; adult)[5]: quality of life measure for adults, that examines 10 domains (46 items) and validated in English. Domains include physical, emotional, social, functional, mental, and treatment-related.

Hemophilia-Specific Quality of Life Index (HAEMO-QOL; caregiver reported for child)6: Quality of life measure for children. This is the parent-reported short version that has a 16-item and a 35-item index for children age 4-7 and 8-17 respectively.

Health Insurance Claims Data Submitted by Patients

- Total services and healthcare costs (healthcare visits, factor)
- Hemophilia-specific services and costs (healthcare visits, factor)

An allocation algorithm for determining how cost groupings will be defined will be developed with discussion with Pfizer.

4.2. Safety Endpoints

This study does not aim to collect data on clinical endpoints on individual patients. However, safety information may be identified during the course of data collection. Any safety information for an individual patient that is volunteered by a study participant (eg, health care professional, lay person) during the course of this research will be reported as described in the study protocol.

4.3. Other endpoints

None.

5. HANDLING OF MISSING VALUES

Complete data from the physician CRF and patient questionnaire are available for all items except those allowing, eg, a "don't know" response. In such cases, if those variables are included as covariates in multivariable models or as outcome measures in bivariate analysis, missing values will be included as a separate, defined category. If those variables are analysed as outcomes, respondents with missing data will be excluded from analysis (and the subsample for analysis will be reported).

6. STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

6.1. Statistical methods

6.1.1. *Descriptive Analyses*

Descriptive statistics (means and standard deviations for continuous variables and frequencies and percentages for categorical variables) will be reported for all study measures on the total sample and subgroups. This analysis of the distributions will be a part of testing of model assumptions and will help inform the appropriate modeling techniques.

6.1.2. *Bivariate Analyses*

Bivariate (BV) comparisons and descriptives can help provide initial insight into the dosing, health-related quality of life, resource utilization, and cost patterns associated with different hemophilia treatments (standard half-life vs. extended half-life). Bivariate comparisons, using chi-square tests or one-way ANOVA for categorical and continuous variables, respectively, will be conducted for each hemophilia subgroup (A and B).

The BV results will be used to feed into a more robust multivariable (MV) analysis to create a model to estimate health-related quality of life, resource utilization and costs, while controlling for covariates, associated with different hemophilia treatments.

6.1.3. *Multivariable Analyses*

Generalized Linear Models

The type of GLM will be chosen on the basis of the distributions of the outcome variables of interest. For example, GLMs specifying a normal distribution and identity function will be used with mostly normally distributed variables (such as is typically the case with SF-36v2 HRQoL measures), whereas GLMs specifying a negative binomial distribution and log-link function will be used with highly positively skewed variables (such as is typically the case with healthcare resource utilization measures). Model fits will be examined to aid with model selection. For example, Poisson models may be attempted first, with highly skewed outcomes, but negative binomial models will also be tested to see if fits improve substantially when including the estimated relationship between mean and variance. Corrections to the standard errors will be implemented automatically to compensate for model underdispersion. In the case of normal distributions, GLMs are recommended, as they are more robust than ordinary least squares (OLS) models to minor deviations from normality.

6.2. Statistical Analyses

6.2.1. *Descriptive Analyses*

Descriptive analyses will serve to characterize the physician sample and the hemophilia A and B sample. Specifically:

- Physician characteristics (eg, medical specialty, percentage of time in patient care) will be examined with means and standard deviations for continuous variables and frequencies and percentages for categorical variables

- Patient characteristics (eg, age, sex, income) will be examined with means and standard deviations for continuous variables and frequencies and percentages for categorical variables

6.2.2. *Bivariate Analyses*

Differences among hemophilia patients on standard half-life vs. extended half-life treatments (hemophilia A: Xyntha vs. Adynovate or Eloctate; hemophilia B: Benefix vs. Alprolix) will be made with respect to demographics variables to assess for potential covariates to include

in subsequent modeling (*Table 2*). Chi-square tests and one-way ANOVAs will be used for categorical and continuous outcomes, respectively. Additionally, differences among treatment groups will also be made with respect to hemophilia specific characteristics (eg, disease severity, symptoms), attitudes towards infusions and physician relationship and outcomes (eg, number of infusions, health-related quality of life, healthcare resource utilization, total healthcare costs, total Rx costs, hemophilia healthcare costs, hemophilia Rx costs) to assess unadjusted differences using one-way ANOVAs (*Table 3*-*Table 7*).

These analyses will be conducted separately for hemophilia A and hemophilia B patients.

Note that healthcare costs and Rx costs will be obtained from claims data and may be limited by sample size as not every patient may be willing to provide that data. If sample sizes are very low, bivariate and multivariable comparisons may not be conducted; descriptive statistics will be provided instead.

Table 2. Example bivariate Table: Patient demographics among hemophilia A patients by standard half-life vs. extended half-life treatment. Note: a similar table would be created for hemophilia B patients.

		Treatment Group						
		Standard Half-Life		**Extended Half-Life**		**Total**		
		% / Mean	N/ SD	% / Mean	N/ SD	% / Mean	N/ SD	p-value
Age								
Gender	Male							
	Female							
Marital Status	Married/partnered							
	Single/divorced/widowed							
	Declined to answer							
Race/Ethnicity	Non-Hispanic White							
	Non-Hispanic Black							
	Hispanic							
	Other ethnicity							
Education	4 years							
	Less than 4 years							
Household income	<25K							
	$25K to <50K							
	$50K to <75K							
	$75K or more							
	Declined to answer							
Employment Status	Employed							
	Not Employed							

Table 2. Example bivariate Table: Patient demographics among hemophilia A patients by standard half-life vs. extended half-life treatment. Note: a similar table would be created for hemophilia B patients.

		Treatment Group						
		Standard Half-Life		**Extended Half-Life**		**Total**		
		% / Mean	N/ SD	% / Mean	N/ SD	% / Mean	N/ SD	p-value
	Student							
Geographic Region	South							
	Northeast							
	Midwest							
	West							
Insurance	Coverage through employer							
	Coverage through spouse's/partner's employer							
	Coverage through parent's or legal guardian's employer							
	Individual/Family Plan-State Health Exchange							
	Individual/Family Plan-Self-purchased							
	Medicaid (MediCal for California)							
	Medicare							
	Veterans Administration (VA)/CHAMPUS							
	TRICARE							
	Not sure							
Healthcare insurer	Aetna							
	Anthem (Blue Cross and Blue Shield, Empire Blue Cross, Amerigroup, UniCare, CareMore, Wellpoint)							
	Centene							
	Cigna							
	Health Net							
	Human							
	Kaiser Permanente							
	Magellan Health							

Table 2. Example bivariate Table: Patient demographics among hemophilia A patients by standard half-life vs. extended half-life treatment. Note: a similar table would be created for hemophilia B patients.

		Treatment Group						
		Standard Half-Life		Extended Half-Life		Total		
		% / Mean	N/ SD	% / Mean	N/ SD	% / Mean	N/ SD	p-value
	Molina Healthcare							
	UnitedHealth Group							
	WellCare Health Plans							
	Other, specify							
Different insurer covering prescription or pharmacy benefits?	Yes, different insurer for prescriptions							
	No, same insurer as medical							
	Don't know							
On patient assistance program for hemophilia medication?	Yes							
	No							
	Don't know							

Table 3. Example bivariate table: Patient health characteristics, disease characteristics, and treatment history among hemophilia A patients by standard half-life vs. extended half-life treatment (from patient chart). Note: a similar table would be created for hemophilia B patients.

		Treatment Group						
		Standard Half-Life		Extended Half-Life		Total		
		% / Mean	N/ SD	% / Mean	N/ SD	% / Mean	N/ SD	p-value
BMI category	BMI: underweight							
	BMI: normal weight							
	BMI: overweight							
	BMI: obese							
	Declined to answer							
When diagnosed with hemophila	Infancy 0-12 months							
	Toddler 1-3 years							
	Preschool 3-5 years							

Table 3. Example bivariate table: Patient health characteristics, disease characteristics, and treatment history among hemophilia A patients by standard half-life vs. extended half-life treatment (from patient chart). Note: a similar table would be created for hemophilia B patients.

		Treatment Group						
		Standard Half-Life		Extended Half-Life		Total		
		% / Mean	N/ SD	% / Mean	N/ SD	% / Mean	N/ SD	p-value
	Grade school 5-12 years Teen 12-18 years							
	Young adult 18-21 years <21 years							
	Don't know							
Comorbidities	Joint disease							
	High blood pressure							
	High cholesterol							
	Heart disease							
	Diabetes							
	HIV							
	Hepatitis							
	Other (specify)							
	None of above							
Currently taking medication for joint disease?	Yes							
	No							
Current disease severity	Moderate hemophilia (1-5% factor level)							
	Severe hemophilia (Less than 1% factor level)							
Current primary symptoms	Excessive bleeding after cuts, injuries, or medical procedures							
	Unexplained nosebleeds Excessive bruising							
	Joint pain, swelling, or tightness							
	Blood in stool or urine							
	Other							
	None of the above							
Current joint	Score							

Table 3. Example bivariate table: Patient health characteristics, disease characteristics, and treatment history among hemophilia A patients by standard half-life vs. extended half-life treatment (from patient chart). Note: a similar table would be created for hemophilia B patients.

		Treatment Group						
		Standard Half-Life		Extended Half-Life		Total		
		% / Mean	N/ SD	% / Mean	N/ SD	% / Mean	N/ SD	p-value
health score	Don't know							
Joint health score system	Hemophilia Joint Health Score (HJHS)							
	World Federation of Hemophilia (WFH) score							
	Other joint scoring system (specify)							
Current factor	Advate							
	Adynovate							
	Afstyla							
	Eloctate							
	Helixate FS							
	Hemofil M							
	Kogenate FS							
	Kovaltry							
	Monoclate-P							
	Novoeight							
	Nuwiq							
	Recombinate							
	Xyntha solofuse							
	Other, specify							
How factor prescribed	Prophylactically							
	On-demand							
	Both prophylactically and on-demand							
Duration of current factor prescribed								
Number of infusions per month								
Prior treatment	Advate							
	Adynovate							
	Afstyla							
	Eloctate							
	Helixate FS							
	Hemofil M							

Table 3. Example bivariate table: Patient health characteristics, disease characteristics, and treatment history among hemophilia A patients by standard half-life vs. extended half-life treatment (from patient chart). Note: a similar table would be created for hemophilia B patients.

		Treatment Group						
		Standard Half-Life		Extended Half-Life		Total		
		% / Mean	N/ SD	% / Mean	N/ SD	% / Mean	N/ SD	p-value
	Kogenate FS							
	Kovaltry							
	Monoclate-P							
	Novoeight							
	Nuwiq							
	Recombinate							
	Other, specify							
	Was not taking another treatment previously							
Duration of former factor prescribed								
Reasons for discontinuation	Cost/insurance coverage issues							
	[IF PATIENT IS UNDER 18] Patient developed inhibitors to treatment							
	Doctor recommendation							
	Patient preferred a different infusion frequency							
	Other							
	Don't know							
Frequency of visits (non-infusion)	Several times a month							
	Once a month							
	Every three months							
	Every six months							
	Once a year							
	Less than once a year							

Table 4. Example bivariate table. Patient health characteristics, disease characteristics, and treatment history among hemophilia A patients by standard half-life vs. extended half-life treatment (patient-reported). Note: a similar table would be created for hemophilia B patients.

		Treatment Group						
		Standard Half-Life		Extended Half-Life		Total		
		% / Mean	N/ SD	% / Mean	N/ SD	% / Mean	N/ SD	p-value
Severity	Mild hemophilia							
	Moderate hemophilia							
	Moderately severe hemophilia							
	Severe hemophilia							
Clotting factor level	6% to 40%							
	1% to 5%							
	Less than 1%							
Current treatment	Advate							
	Adynovate							
	Afstyla							
	Eloctate							
	Helixate FS							
	Hemofil M							
	Kogenate FS							
	Kovaltry							
	Monoclate-P							
	Novoeight							
	Nuwiq							
	Recombinate							
	Xyntha solofuse							
	Other, specify							
Duration of current factor prescribed								
When infuse	On regular basis to prevent bleeding episodes							
	Whenever or as needed when there is a bleeding episode							
	Both, on a regular basis to prevent bleeding episodes as well as whenever as needed when there is a bleeding episode							
Prior treatment	Advate							
	Adynovate							

Table 4. Example bivariate table. Patient health characteristics, disease characteristics, and treatment history among hemophilia A patients by standard half-life vs. extended half-life treatment (patient-reported). Note: a similar table would be created for hemophilia B patients.

		Treatment Group						
		Standard Half-Life		Extended Half-Life		Total		
		% / Mean	N/ SD	% / Mean	N/ SD	% / Mean	N/ SD	p-value
	Afstyla							
	Eloctate							
	Helixate FS							
	Hemofil M							
	Kogenate FS							
	Kovaltry							
	Monoclate-P							
	Novoeight							
	Nuwiq							
	Recombinate							
	Other, specify							
	Was not taking another treatment previously							
Duration of former factor prescribed								
Clinical trials for receiving treatment	Yes							
	No							

Table 5. Example bivariate table. Health-related quality of life among hemophilia A patients by standard half-life vs. extended half-life treatment (patient-reported). Note: a similar table would be created for hemophilia B patients.

	Treatment Group						
	Standard Half-Life		Extended Half-Life		Total		
	Mean	SD	Mean	SD	Mean	SD	p-value
for adults							
SF-36 Physical Component Summary Score							
SF-36 Mental Component Summary Score							
HAEM-A-QOL)							
caregiver reported for child							
SF-10 Physical summary score							
SF-10 Psychosocial health summary score							
HAEMO-QOL							

Table 6. Example bivariate table. Patients' attitudes on factor use and physician relationship among hemophilia A patients by standard half-life vs. extended half-life treatment. Note: a similar table would be created for hemophilia B patients.

		Treatment Group						
		Standard Half-Life		Extended Half-Life		Total		
		%	N	%	N	%	N	p-value
Frequency of extra infusion used	Never 2 times 3 times 4 times or more							
Reasons for using extra infusion	Bleeding episode Wanted additional protection before sport/activity Felt pain (thought it was bleed) Wanted extra protection for no specific reason							
Frequency of dose higher than prescribed	Never 1-2 times 3-4 times 5-6 times 7 or more times							
Reasons for higher dosing	Wanted additional protection before sport/activity Felt pain (thought it was bleed) Wanted extra protection for no specific reason							
Physician relationship	The physician is the professional; 'I' / 'we' follow his/her recommendations. 'I' / 'We' see the physician as the expert who knows what's best for 'me' / 'my child'. The physician makes the final decision.							

	The physician informs 'me' / 'me and my child' of the different treatment plans available to 'me' / 'my child' and lets 'me' / 'us' select the final treatment. The physician provides technical expertise but 'I' / 'we' make the final decision on treatment.							
	The physician works with 'me' / 'me and my child' to understand 'my' / 'our' values and what 'I' / 'we' want out of the treatment and then discusses the different treatment options available to 'me' / 'us' based on 'my' / 'our' needs before we make the joint decision for 'me' / 'my child'. 'I' / 'We' see the physician as a counselor.							
	The physician works with 'me' / 'us' to understand 'my' / 'our' values and what 'I' / 'we' want out of the treatment, and goes over all 'my' / 'our' treatment options and his/her recommendations so that 'I' / 'we' can make the best possible decision. 'I' / 'We' see the physician as a teacher or friend.							

Table 7. Example bivariate table. Healthcare resource use and associated costs among hemophilia A patients by standard half-life vs. extended half-life treatment (insurance-claims). Note: a similar table would be created for hemophilia B patients.

	Treatment Group						
	Standard Half-Life		Extended Half-Life		Total		
	Mean	SD	Mean	SD	Mean	SD	p-value
Total number of healthcare visits							
Total number of healthcare costs							
Total Rx costs							
Total number of Hemophilia-specfic visits							
Total number of Hemophilia-specfic costs							
Total Hemophilia Rx costs							

6.2.3. *Multivariable Analyses*

For hemophilia A and hemophilia B cohorts separately, multivariable regression models will be conducted with treatment group (standard half-life vs. extended half-life) as the predictor of each outcome (ie, number of infusions, health-related quality of life, healthcare resource utilization, total healthcare costs, total Rx costs, hemophilia healthcare costs, hemophilia Rx costs) adjusting for the demographic and health history variables that have been identified as relevant covariates in bivariate analyses.

Generalized linear models will be used specifying the appropriate distribution (ie, negative binomial for skewed variables such as healthcare resource use and cost variables; identity link function for normally distributed variables such as health-related quality life). A regression summary results table with adjusted means, 95% CIs, standard errors, and p-values will be produced (*Table 8*).

Table 8. Example regression summary table. Outcomes among hemophilia A patients by standard half-life vs. extended half-life treatment (adjusted for covariates). Note: a similar table would be created for hemophilia B patients.

	Standard Half-Life				Extended Half-Life				
Outcome	**Mean**	**SE**	**Lower 95% CI**	**Upper 95% CI**	**Mean**	**SE**	**Lower 95% CI**	**Upper 95% CI**	**p-value**
Number of infusions per month									
SF-36 MCS/ SF-10 psychosocial									
SF-36 PCS / SF-10 physical									
HEAM-A-QOL / HAEMO-QOL									
Total Healthcare visits									
Total Healthcare costs									
Total Rx costs									
Hemophilia healthcare visits									
Hemophilia healthcare costs									
Hemophilia Rx costs									

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