NON-INTERVENTIONAL (NI) STUDY PROTOCOL

[redacted]

Study informations

Title	Understanding Hemophilia A and B Drug Dosage Administration Patterns
Protocol number	B1821056
Protocol version identifier	Version 1.1
Date of last version of protocol	04 April 2017
Active substance	B02BD09 – nonacog alfa B02BD04 – coagulation Factor IX B02BD31 – moroctocog alfa B02BD02 – coagulation factor VIII
Medicinal product	Coagulation Factor VIII and Factor IX products
Research question and objectives	To compare the real world administration patterns and resource utilization implications of standard half-life (BeneFIX for hemophilia B, Xyntha and other standard half-life agents for hemophilia A) vs extended half-life (Alprolix for hemophilia B, Eloctate and Adynovate for hemophilia A) agents for the treatment of hemophilia.
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INVESTIGATOR SIGNATURE PAGE

I have reviewed and approved Protocol B1821056. By signing below, I agree to abide by the terms of the protocol.

Signature: _____

Name: _____

Title: _____

Institution: _____

Date: _____

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AEM	Adverse Event Monitoring
ANOVA	Analysis of Variance
BV	Bivariate
CRF	Chart Review Form
EDP	Exposure During Pregnancy
FDA	Food and Drug Administration
GLM	General Linear Model
HAEM-A-QOL	Hemophilia-Specific Quality of Life Index for Adults
HAEMO-QOL	Hemophilia-Specific Quality of Life Index
ID	Identification
IRB / IEC	Institutional Review Board / Independent Ethics Committee
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
MDE	Minimum Detectable Effect
MV	Multivariate
NIS	Non-interventional Study
OLS	Ordinary Least Squares
PI/Sub-PI	Primary Investigator/ Sub-Primary Investigator
SAP	Statistical Analysis Plan
SAE	Serious Adverse Event

SAS	Statistical Analysis System
SF-36	36 Item Short Form Health Survey
SF-10	10 Item Short Form Health Survey
SOPs	Standard Operating Procedures
SPSS	Statistical Package for the Social Sciences
US	United States

2. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

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3. ABSTRACT

- **Title:** Understanding Hemophilia A and B Drug Dosage Administration Patterns. Version 4.0, 16 March 2017

- **Rationale and background:** In recent years newer and extended half-life treatments (e.g. Alprolix, Eloctate, Adynovate) for hemophilia have been approved by the Food and Drug Administration (FDA). These newer, extended half-life treatments require less frequent administrations than standard half-life treatments (e.g. BeneFIX, Xyntha). However, little is known about the real world administration patterns for extended half-life treatments in comparison to standard half-life treatments.

- **Research question and objectives:** To compare the real world administration patterns and resource utilization associated with of standard half-life (e.g. BeneFIX for hemophilia B, Xyntha for hemophilia A) vs extended half-life (e.g. Alprolix for hemophilia B, Eloctate and Adynovate for hemophilia A) agents for the treatment of hemophilia in the U.S.

- **Study design:** This will be a U.S. site-based study in which physician sites are recruited to participate in the study and enroll patients. Participating physicians will conduct a chart review for their enrolled patients and these same patients will respond to a patient questionnaire online via a web survey. In addition, these patients will be consented to supply their insurance claims data to Kantar Health study team for analysis. All survey questionnaires will be in English.

- **Population:** Approximately 30 sites will participate in this study, with 300 patients enrolled (some caregivers expected if eligible patient is under 18 years of age). The approximate distribution of patients by hemophilia type and treatment type is as follows:

- Hemophilia A patients currently receiving Xyntha or another standard half-life treatment for at least six months (n=~75).

- Hemophilia A patients currently receiving Adynovate or Eloctate for at least six months AND have been switched from a standard half-life treatment, and have been on the prior SHL treatment for at least six months (n=~75).

- Hemophilia B patients currently receiving BeneFIX for at least six months (n=~75).

- Hemophilia B patients currently receiving Alprolix for at least six months AND have been switched from BeneFIX, and have been on the prior BeneFIX treatment for at least six months (n=~75).

- **Variables:** Include physician/practice characteristics, patient treatment pattern, patient demographics and patient clinical profile to be collected in the chart review form (CRF); patient demographics, clinical profile, physician-patient relationship, and quality of life reported outcomes to be collected in the patient/caregiver reported questionnaire; and

cost and utilization related to overall health and hemophilia management to be retrieved from claims data provided by patients/caregivers.

- **Data sources:** Study data will come from three sources: (1) the patient/caregiver-reported outcomes and treatment patterns collected in the form of an online survey, (2) the CRF by physicians collected in the form of an online survey, and (3) the data extracted from patient medical and pharmacy claims which will be received as paper files or pdf downloads.

- **Study size:** This study will involve approximately 30 sites and approximately 300 patients. Eligible sites will be activated on an ongoing basis and evaluated continuously as necessary to achieve cohort fulfillment.

- **Data analysis:** Descriptive statistics (means, standard deviations, frequencies, percentages) will be used to characterize the physician and patient sample. Bivariate analyses using one-way Analysis of Variance (ANOVA) or chi-square tests will compare differences in demographics, health characteristics and outcomes (i.e., dosing, disease severity, health-related quality of life, healthcare resource use, costs) between standard half-life vs. extended half-life treatments separately for hemophilia A and hemophilia B patient cohorts. Generalized linear models (with appropriate link function and distribution) will be used to compare outcomes by treatment groups, adjusting for covariates.

- **Milestones:** This study is estimated to take 18 months to complete with final report tentatively expected in late 2018.

4. AMENDMENTS AND UPDATES

The protocol has been amended to incorporate the feedback received from the initial feasibility part of this study. Safety language has been amended to reflect the nature of data capture and participant interaction, and to ensure compliance with the required safety reporting Standard Operating Procedures (SOPs).

5. MILESTONES

Milestone	Planned date
Start of data collection	April 2017
End of data collection	December 2017
Study Close Out	October 2018

6. RATIONALE AND BACKGROUND

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, extended half-life treatments for hemophilia have recently been approved by the FDA). Alprolix is an extended half-life treatment 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, extended half-life 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 extended half-life 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 extended half-life products compared with the standard half-life products. To date, little is known about real world administration patterns for extended half-life treatments in comparison to standard half-life treatments. Pfizer is seeking to understand whether 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.

7. RESEARCH QUESTION AND 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 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

8. RESEARCH METHODS

8.1. 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.

8.2. Setting

The study will occur in a site-based clinical practice setting, meaning that patients will be recruited by physicians to participate in the study. Eligible sites will be activated on an ongoing basis and evaluated continuously as necessary to achieve cohort fulfillment. Sites will identify patients according to criteria specified within protocol and patients will further be qualified within the web questionnaire. The Kantar Health research team will closely monitor patient enrollment between sites to ensure equal distribution across the four cohorts is achieved. If needed, additional sites will be contracted and activated to meet total cohort sample size. All physician and patient materials will be completed online via a web-link to a survey provided by Kantar Health.

8.2.1. Inclusion criteria

Physician/Clinician Participants

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 (e.g. 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

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

1. 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.

8.2.2. Exclusion criteria

Patient Participants

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

8.3. Variables

Below is the current list of variables to be assessed in the in the study:

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

- 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 Clinical Profile

- Height and Weight;
- Age of diagnosis;
- Primary symptoms;
- Disease severity;
- Joint health score;
- Comorbidities.

Patient Participants:

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

- 36 Item Short Form Health Survey (SF-36 (adult)).[3]
- 10 Item Short Health Survey (SF-10 (caregiver reported for child)).[4]
- Hemophilia-Specific Quality of Life Index for Adults (HAEM-A-QOL (adult)).[5]
- Hemophilia-Specific Quality of Life Index (HAEMO-QOL (caregiver reported for child)).[6]

Health Insurance Claims Data from Patients

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

8.4. Data sources

This study will be conducted with physicians and patients in an online setting. Prior to participating, patients will be asked to provide their informed consent in order to proceed with the web surveys and provision of their health care insurance claims.

The physicians participating in this research will be asked to reference their patient medical records for each enrolled patient during their portion of the study.

There will be three sources of data for each patient (or caregivers of patients in the case of minor patients):

- Patient responses to a web survey/questionnaire

- Physician responses to a CRF concerning the same patient

- Patients' medical and pharmacy claims data obtained directly by the patient from their healthcare insurer and provided to Kantar Health via a secure, dedicated email address.

No personal identifiable information will be captured in either the CRF or patient questionnaire. However, the medical claims component of the patient data may include confidential information. Therefore, we will ensure that all personal identifiable data are removed from the claims when the claims are received by Kantar Health. Once Kantar Health study staff receives claims via the dedicated email address, all identifying information (name, date of birth, or other individual identifiers) are redacted using mark-up application that puts a black bar over this data. The claims document is then numbered with the patient's anonymous study ID number and saved using the study ID number as the document name. The document is also password protected so that the redacting masks cannot be removed by other individuals. All patient data will be reported in aggregate form and participants will only be identified by a random unique ID for reference. Kantar Health will not link any study data to personal information of any patient or physician participant.

It is anticipated that claims data received will vary in type and degree of insurance data across different insurers. As such, the planned process is to extract some of the common variables as seen within sample claims such as date of service, carrier, provider type, service description, cost, and any procedural or diagnosis codes if present. The data will be entered and validated by Kantar Health. Final variable list and data format will be discussed with Pfizer prior to data entry.

8.5. Study size

The study will involve approximately 300 patients recruited from approximately 30 participating sites.

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.

8.6. Data management

Study data will come from three sources: (1) the patient-reported outcomes and treatment patterns collected in the form of an online survey, (2) the CRF by physicians collected in the form of an online survey, and (3) the data extracted from patient medical and pharmacy claims which will be receive as paper files or pdf downloads.

Both patient and physician participants will be entering their survey responses via survey links that are unique to each participant so that each participant is identified by a random unique identification (ID) number. The database which houses the survey responses allows for direct exportation into statistical software (e.g., Statistical Package for the Social Sciences (SPSS), Statistical Analysis System (SAS), Stata). Because each participant will be identified by a random unique ID number, the working data files will not contain any identifying information apart from the ID number. No identifying information (e.g. names, addresses, or other distinguishing information) will collected in the surveys will not be designed with such variables in mind.

Regarding the claims data, a dedicated email address for receiving this data will be set up to receive this data directly from the patients (?) for this particular study to be accessed only by a select group of the research team at Kantar Health. Any personal identifiable data available in the claims, such as names, dates of birth, social security numbers, etc., will be omitted during data entry (performed through an external coding vendor) and all participants will only be identified by an assigned random unique ID for reference. Furthermore, the original claims data will be saved for 24 months after study completion and then backed up / destroyed according to Pfizer requirements. The file containing claims data will be created in an agreed upon format between Pfizer and the Kantar Health. Data files provided to the broader Kantar Health research team or Sponsor will not include any personal identifying information as this information is either not collected or have been omitted/redacted as indicated above to preserve confidentiality. Details of data entry management are contained in the Data Management Plan.

8.7. Data analysis

A detailed description of the analyses for this study will be provided in a statistical analysis plan (SAP). Below are the general statistical approaches we will implement.

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.

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). BV comparisons, using chi-square tests or one-way Analysis of Variance (ANOVA) for categorical and continuous variables, respectively, will be conducted for each hemophilia subgroup.

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.

Multivariable Analyses

Generalized Linear Models (GLM)

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 Health Related Quality of Life 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.

8.8. Quality control

For this study, double data entry will be conducted for 15% of the total data entered. As there will be a total of 300 patients enrolled in the study, 45 patients' responses will be randomly selected and all data for those patients will undergo double data entry in a separate excel file. Once all data is entered and double data entry has been completed, a comparison will be made within excel to address any discrepancies. If the error rate is higher than 10%, then 100% of the data will be verified. Prior to data collection or data entry, consistency of database format will be confirmed for all data types.

Details of the number of respondents chosen for data verification, how these were selected and the acceptable error level must be documented with the study documentation. Details of errors found, and what actions were taken following the discovery of these errors will be documented in the Data Entry Log. Of note, the only data entry activities for this study include entering the data from the patient's medical claims data.

All of the patient's medical claims data collected on paper will be stored on site at a Kantar facility in Toledo, Ohio. The data will be stored in a locked room that only the project team has access to. The data will be saved for 24 months after study completion and then backed up / destroyed according to Pfizer requirements.

8.9. Limitations of the research methods

Subject responses may be influenced by recall and self-presentation biases which could introduce additional error. Therefore the design of the study was approached with the intent to maximize the external validity of the findings by requesting patient's medical claims (as opposed to asking them to self-report their healthcare resource utilization for the past 12 months, which will require recall and estimation) and obtaining real-world medical records data via the CRFs from physician report.

8.10. Other aspects

Not applicable.

9. PROTECTION OF HUMAN SUBJECTS

9.1. Participant Information and Consent

All parties will ensure protection of patient personal data and will not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. In case of data transfer, Pfizer will maintain high standards of confidentiality and protection of patient personal data.

As this study will be conducted at participating sites, all sites will be thoroughly trained on the informed consent procedures for the study prior to beginning patient enrollment. Sites will be trained that each patient (or their caregiver) must autonomously consent to participate in the study prior to conducting the patient chart review or the patient participating in any study procedures. In the case of minors ages 12-18, in addition to the parent/caregiver providing their informed consent, the minor will sign an assent document confirming their understanding and agreement of their role in the study. Specifically, the minor will be informed that their parent/caregiver will be filling out a survey on the minor's behalf as well as submitting the minor's claims data and that the doctor will be performing a chart review of the minor's medical chart. The use of the assent form will verify that older minors – while not legally able to provide informed consent - are informed of the study procedures regarding their personal information, and respects their autonomy and privacy by allowing them to either agree or decline their participation on this basis. The informed consent and assent forms used in this study, and any changes made during the course of the study, must be prospectively approved by both the IRB/IEC and Pfizer before use. Kantar Health will obtain central IRB review and approval for this study in the case of sites that allow central IRB

approval. However, some participating sites may require their local site IRB review and approve the study and the consent documents per institution requirements. In these cases, the participating site will use the relevant institution-specific informed consent template for the study, however all site-specific consent documents must be approved by Kantar Health and Pfizer prior to use. In addition, sites may not make amendments to the informed consent documents with the approval of Pfizer and Kantar Health.

9.2. Participant withdrawal

Participants may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the site investigator. In any circumstance, every effort should be made to document subject outcome, if possible.

If the participant withdraws from the study, and also withdraws consent for disclosure of future information, no further evaluations should be performed, and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

9.3. Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

Kantar Health will be responsible for obtaining approval of the study protocol, protocol amendments, and informed consent forms, and other relevant documents, (e.g., recruitment advertisements), if applicable, from the IRB/IEC. Copies of IRB/IEC approvals can forwarded to Pfizer should sponsor want. Dependent upon the policies of each participating site, local IRB approval may be required at some of the sites whereas some sites are able to accept central IRB approval as the IRB of record for this study. The site's requirements for local or central IRB will be determined at the site contracting stage and agreed upon during the contracting process with each site.

9.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR). IRB approval will be collected from a central IRB or local IRB as described above prior to starting data collection.

10. MANAGEMENT AND REPORTING OF ADVERSE EVENTS (AE)/ADVERSE REQUIREMENTS

10.1. Adverse Event Reporting during Claims Assistance

This study does not involve data collection of prospective, clinically adjudicated endpoints on individual patients. There is no mechanism by which information on safety events for an individual patient will be captured by a study participant during the course of claims data collection; However, any information on a safety event inadvertently volunteered by a study participant during the course of this research must be reported as described as part of Your Reporting Responsibilities for contract research associations for non-interventional studies.

Further, routine communication with study participants via email or phone with the project team at Kantar Health is not expected during the conduct of the study. However, it is possible that a study participant may provide information that could constitute a safety event (e.g., serious and non-serious AEs and/or scenarios involving exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure) to project team while in conversation about the survey for any other reason (e.g., seeking information about the purpose of the study). In the event that a study participant in the study reports a safety event associated with the use of the Pfizer product, the project team will complete a non-interventional study (NIS) adverse event monitoring (AEM) Report Form and submit to Pfizer within 24 hours of becoming aware of the safety event. Included in the completion of the NIS AEM Report Form is the study participant's contact information as the reporter, as well as the contact information for the applicable primary healthcare provider; complete contact information should be obtained so that, once the NIS AEM Report Form is transferred to Pfizer, the NIS AEM Report Form will be assessed and processed according to Pfizer's standard operating procedures, including requests for follow-up regarding the safety event to the study participant, or as appropriate, the individual patient's primary healthcare provider.

All members of the project team at Kantar Health will complete the Pfizer requirements regarding training on the following: "Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)" and any relevant Your Reporting Responsibilities supplemental training. This training must be completed by the project team prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer. In the event that study conduct will be longer than 1 year, re-training will be completed on an annual basis using the most current "Your Reporting Responsibilities" training materials.

Incidental collection of AE or Serious Adverse Events (SAE) for Non-Pfizer product information should NOT be reported to Pfizer Safety Database while reviewing data from any source

10.2. Guidance For Investigators AE Reporting during completion of Investigators Survey Questionnaire

The table below summarizes the requirements for recording safety events on the case report form and for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety. These requirements are delineated for three types of events: (1) serious adverse events (SAEs); (2) non-serious AEs (as applicable); and (3) scenarios involving exposure to a Pfizer product, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, and occupational exposure. These events are defined in the section "Definitions of safety events".

Safety event	Recorded on the Case Report Form	Reported on the NIS AEM Report Form to Pfizer Safety within 24 hours of awareness
SAE	All (regardless of whether the event is determined by the investigator to be related to any Pfizer product)	Only events determined by the investigator to be related to a Pfizer product
Non-serious AE	All (regardless of whether the event is determined by the investigator to be related to any Pfizer product)	None
Scenarios **involving exposure to a Pfizer product**, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation; lack of efficacy; and occupational exposure	All (regardless of whether associated with an AE), **except occupational exposure**	All (regardless of whether associated with an AE) involving exposure to a Pfizer product

For each AE, the investigator must pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a SAE (see section "Serious Adverse Events" below)

Safety events must be reported to Pfizer within 24 hours of awareness of the event by the investigator as described in the table above. In particular, if the SAE is fatal or life-threatening, notification to Pfizer must be made immediately, irrespective of the extent of available event information. This timeframe also applies to additional new (follow-up) information on previously forwarded safety event reports. In the rare situation that the investigator does not become immediately aware of the occurrence of a safety event, the investigator must report the event within 24 hours after learning of it and document the time of his/her first awareness of the events.

For those safety events that are considered serious or that are identified in the far right column of the table above that are reportable to Pfizer within 24 hours of awareness, the investigator is obligated to pursue and to provide any additional information to Pfizer in accordance with this 24-hour timeframe. In addition, an investigator may be requested by Pfizer to obtain specific follow-up information in an expedited fashion. This information is more detailed than that recorded on the case report form. In general, this will include a description of the adverse event in sufficient detail to allow for a complete medical assessment of the case and independent determination of possible causality. Information relevant to the event, such as concomitant medications and illnesses must be provided. In the case of a patient death, a summary of available autopsy findings must be submitted as soon as possible to Pfizer or its designated representative.

Reporting period

For each patient, the safety event reporting period begins at the time of the patient's informed consent, which is obtained prior to the patient's enrollment in the study, and lasts through the end of the observation period of the study; a report must be submitted to Pfizer Safety (or its designated representative) for any of the types of safety events listed in the table above occurring during this period. Most often, the date of informed consent is the same as the date of enrollment. In some situations, there may be a lag between the dates of informed consent and enrollment. In these instances, if a patient provides informed consent but is never enrolled in the study (e.g., patient changes his/her mind about participation, failed screening criteria), the reporting period ends on the date of the decision to not enroll the patient. If the investigator becomes aware of a SAE occurring at any time after completion of the study and s/he considers the serious AE to be related to a Pfizer product, the SAE also must be reported to Pfizer Safety.

Causality assessment

The investigator is required to assess and record the causal relationship. For all AEs, sufficient information should be obtained by the investigator to determine the causality of each adverse event. For AEs with a causal relationship to a Pfizer product, follow-up by the investigator is required until the event and/or its sequelae resolve or stabilize at a level acceptable to the investigator, and Pfizer concurs with that assessment.

An investigator's causality assessment is the determination of whether there exists a reasonable possibility that a Pfizer product caused or contributed to an adverse event. If the investigator's final determination of causality is "unknown" and s/he cannot determine whether a Pfizer product caused the event, the safety event must be reported within 24 hours.

If the investigator cannot determine the etiology of the event but s/he determines that a Pfizer product did not cause the event, this should be clearly documented on the case report form and the NIS AEM Report Form.

DEFINITIONS OF SAFETY EVENTS

Adverse events

An AE is any untoward medical occurrence in a patient administered a medicinal product. The event need not necessarily have a causal relationship with the product treatment or usage. Examples of adverse events include but are not limited to:

- Abnormal test findings (see below for circumstances in which an abnormal test finding constitutes an adverse event);
- Clinically significant symptoms and signs;
- Changes in physical examination findings;
- Hypersensitivity;
- Progression/worsening of underlying disease;
- Lack of efficacy;
- Drug abuse;
- Drug dependency.

Additionally, for medicinal products, they may include the signs or symptoms resulting from:

- Drug overdose;
- Drug withdrawal;
- Drug misuse;
- Off-label use;
- Drug interactions;
- Extravasation;
- Exposure during pregnancy;
- Exposure during breast feeding;
- Medication error;
- Occupational exposure.

Abnormal test findings

The criteria for determining whether an abnormal objective test finding should be reported as an adverse event are as follows:

Test result is associated with accompanying symptoms, and/or

Test result requires additional diagnostic testing or medical/surgical intervention, and/or

Test result leads to a change in study dosing or discontinuation from the study, significant additional concomitant drug treatment, or other therapy, and/or

Test result is considered to be an adverse event by the investigator or sponsor.

Merely repeating an abnormal test, in the absence of any of the above conditions, does not constitute an adverse event. Any abnormal test result that is determined to be an error does not require reporting as an adverse event.

Serious adverse events

A serious adverse event is any untoward medical occurrence in a patient administered a medicinal or nutritional product (including pediatric formulas) at any dose that:

Results in death;

Is life-threatening;

Requires inpatient hospitalization or prolongation of hospitalization (see below for circumstances that do not constitute adverse events);

Results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);

Results in congenital anomaly/birth defect.

Medical and scientific judgment is exercised in determining whether an event is an important medical event. An important medical event may not be immediately life-threatening and/or result in death or hospitalization. However, if it is determined that the event may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Additionally, any suspected transmission via a Pfizer product of an infectious agent, pathogenic or non-pathogenic, is considered serious. The event may be suspected from clinical symptoms or laboratory findings indicating an infection in a patient exposed to a

Pfizer product. The terms "suspected transmission" and "transmission" are considered synonymous. These cases are considered unexpected and handled as serious expedited cases by PV personnel. Such cases are also considered for reporting as product defects, if appropriate.

Hospitalization

Hospitalization is defined as any initial admission (even if less than 24 hours) to a hospital or equivalent healthcare facility or any prolongation to an existing admission. Admission also includes transfer within the hospital to an acute/intensive care unit (e.g., from the psychiatric wing to a medical floor, medical floor to a coronary care unit, neurological floor to a tuberculosis unit). An emergency room visit does not necessarily constitute a hospitalization; however, an event leading to an emergency room visit should be assessed for medical importance.

Hospitalization in the absence of a medical AE is not in itself an AE and is not reportable. For example, the following reports of hospitalization without a medical AE are not to be reported.

Social admission (e.g., patient has no place to sleep)

Administrative admission (e.g., for yearly exam)

Optional admission not associated with a precipitating medical AE (e.g., for elective cosmetic surgery)

Hospitalization for observation without a medical AE

Admission for treatment of a pre-existing condition not associated with the development of a new AE or with a worsening of the pre-existing condition (e.g., for work-up of persistent pre-treatment lab abnormality)

Protocol-specified admission during clinical study (e.g., for a procedure required by the study protocol)

Scenarios necessitating reporting to Pfizer Safety within 24 hours

Scenarios involving exposure during pregnancy, exposure during breastfeeding, medication error, overdose, misuse, extravasation, lack of efficacy, and occupational exposure are described below.

Exposure during pregnancy

An exposure during pregnancy (EDP) occurs if:

A female becomes, or is found to be, pregnant either while receiving or having been exposed to (e.g., environmental) a Pfizer product, or the female becomes, or is found to be, pregnant after discontinuing and/or being exposed to a Pfizer product (maternal exposure).

An example of environmental exposure would be a case involving direct contact with a Pfizer product in a pregnant woman (e.g., a nurse reports that she is pregnant and has been exposed to chemotherapeutic products).

A male has been exposed, either due to treatment or environmental exposure to a Pfizer product prior to or around the time of conception and/or is exposed during the partner pregnancy (paternal exposure).

As a general rule, prospective and retrospective exposure during pregnancy reports from any source are reportable irrespective of the presence of an associated AE and the procedures for SAE reporting should be followed.

If a study participant or study participant's partner becomes, or is found to be, pregnant during the study participant's treatment with a Pfizer product, this information must be submitted to Pfizer, irrespective of whether an adverse event has occurred, must be submitted using the NIS AEM Report Form and the EDP Supplemental Form.

In addition, the information regarding environmental exposure to a Pfizer product, in a pregnant woman (e.g., a subject reports that she is pregnant and has been exposed to a cytotoxic product by inhalation or spillage) must be submitted using the NIS AEM Report Form and the EDP supplemental form. This must be done irrespective of whether an AE has occurred.

Information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

Follow-up is conducted to obtain general information on the pregnancy, in addition, follow-up is conducted to obtain information on EDP outcome for all EDP reports with pregnancy outcome unknown. A pregnancy is followed until completion or until pregnancy termination (e.g., induced abortion) and Pfizer is notified of the outcome. This information is provided as a follow up to the initial EDP report. In the case of a live birth, the structural integrity of the neonate can be assessed at the time of birth. In the event of a termination, the reason(s) for termination should be specified and, if clinically possible, the structural integrity of the terminated fetus should be assessed by gross visual inspection (unless pre-procedure test findings are conclusive for a congenital anomaly and the findings are reported).

If the outcome of the pregnancy meets the criteria for an SAE (e.g., ectopic pregnancy, spontaneous abortion, intrauterine fetal demise, neonatal death, or congenital anomaly [in a live born, a terminated fetus, an intrauterine fetal demise, or a neonatal death]), the procedures for reporting SAEs should be followed.

Additional information about pregnancy outcomes that are reported as SAEs follows:

Spontaneous abortion includes miscarriage and missed abortion;

Neonatal deaths that occur within 1 month of birth should be reported, without regard to causality, as SAEs. In addition, infant deaths after 1 month should be reported as SAEs when the investigator assesses the infant death as related or possibly related to exposure to investigational product

Additional information regarding the exposure during pregnancy may be requested. Further follow-up of birth outcomes will be handled on a case-by-case basis (e.g., follow-up on preterm infants to identify developmental delays).

In the case of paternal exposure, the study participant will be provided with the Pregnant Partner Release of Information Form to deliver to his partner. It must be documented that the study participant was given this letter to provide to his partner.

Exposure during breastfeeding

Scenarios of exposure during breastfeeding must be reported, irrespective of the presence of an associated AE. An exposure during breastfeeding report is not created when a Pfizer drug specifically approved for use in breastfeeding women (e.g., vitamins) is administered in accord with authorized use. However, if the infant experiences an AE associated with such a drug's administration, the AE is reported together with the exposure during breastfeeding.

Medication error

A medication error is any unintentional error in the prescribing, dispensing or administration of a medicinal product that may cause or lead to inappropriate medication use or patient harm while in the control of the health care professional, patient, or consumer. Such events may be related to professional practice, health care products, procedures, and systems including: prescribing; order communication; product labeling, packaging, and nomenclature; compounding; dispensing; distribution; administration; education; monitoring; and use.

Medication errors include:

Near misses, involving or not involving a patient directly (e.g., inadvertent/erroneous administration, which is the accidental use of a product outside of labeling or prescription on the part of the healthcare provider or the patient/consumer);

Confusion with regard to invented name (e.g., trade name, brand name).

The investigator must submit the following medication errors to Pfizer, irrespective of the presence of an associated AE/SAE:

Medication errors involving patient exposure to the product, whether or not the medication error is accompanied by an AE.

Medication errors that do not involve a patient directly (e.g., potential medication errors or near misses). When a medication error does not involve patient exposure to the product the following minimum criteria constitute a medication error report:

An identifiable reporter;

A suspect product;

The event medication error.

Overdose, Misuse, Extravasation

Reports of overdose, misuse, and extravasation associated with the use of a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

Lack of Efficacy

Reports of lack of efficacy to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE or the indication for use of the Pfizer product.

Occupational Exposure

Reports of occupational exposure to a Pfizer product are reported to Pfizer by the investigator, irrespective of the presence of an associated AE/SAE.

10.3. Adverse Event Reporting Guidance for Patient and/or Caregiver Survey Responses

The patient questionnaire for this study will be completed online via a secure website. The online surveys do not include questions that could potentially identify a safety event, nor does it provide a free text field where study participants could specify information that may constitute a safety event. Responses indicative of "bleeding" and / or "pain" reported through the patient completed closed item questionnaire < see **ANNEX 2**> are considered hemophilia events that are related to the condition of hemophilia, or directly as a consequence of the bleeding event and are not considered as an adverse event and reportable.

REQUIREMENTS

This study does not involve data collection on clinical endpoints on individual patients. There is no mechanism by which information on safety events for an individual patient will be captured by a study participant during the course of data collection; thus reporting of adverse events is not feasible in the data collection process. However, any information on a safety event inadvertently volunteered by a study participant during the course of this research must be reported as described below.

The survey CRF for this study will be completed online via a secure website. The survey does not include questions that could potentially identify a safety event, nor does it provide a free text field where study participants could specify information that may constitute a safety event. Further, routine communication with study participants via email or phone with the Programme staff is not expected during the conduct of the study. However, it is possible that a study participant may provide information that could constitute a safety event (e.g., serious and non-serious AEs and/or scenarios involving exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure) to Programme staff while in conversation about the survey CRF for any other reason (e.g., seeking information about the purpose of the study). In the event that a study participant in the study reports a safety event associated with the use of the Pfizer product, the Programme staff will complete a non-interventional study (NIS) adverse event monitoring (AEM) Report Form and submit to Pfizer within 24 hours of becoming aware of the safety event. Included in the completion of the NIS AEM Report Form is the study participant's contact information as the reporter, as well as the contact information for the applicable primary healthcare provider; complete contact information should be obtained so that, once the NIS AEM Report Form is transferred to Pfizer, the NIS AEM Report Form will be assessed and processed according to Pfizer's standard operating procedures, including requests for follow-up regarding the safety event to the study participant, or as appropriate, the individual patient's primary healthcare provider..

All Programme staff will complete the Pfizer requirements regarding training on the following: "*Your Reporting Responsibilities: Monitoring the Safety, Performance and Quality of Pfizer Products (Multiple Languages)"* and any relevant Your Reporting Responsibilities supplemental training. This training must be completed by the Programme staff prior to the start of data collection. All trainings include a "Confirmation of Training Certificate" (for signature by the trainee) as a record of completion of the training, which must be kept in a retrievable format. Copies of all signed training certificates must be provided to Pfizer.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Following the conclusion of patient recruitment, Kantar Health will provide Pfizer with a final summary report of the study findings. A summary will be made available to a participant upon request.

For all publications relating to the Study, Pfizer will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

11.1. Publications by Investigators

Pfizer has no objection to publication by Investigator of any information collected or generated by Investigator, whether or not the results are favorable to the Investigational Drug. However, to ensure against inadvertent disclosure of Confidential Information or

unprotected Inventions, Investigator will provide Pfizer an opportunity to review any proposed publication or other type of disclosure before it is submitted or otherwise disclosed.

Investigator will provide manuscripts, abstracts, or the full text of any other intended disclosure (poster presentation, invited speaker or guest lecturer presentation, etc.) to Pfizer at least 30 days before they are submitted for publication or otherwise disclosed. If any patent action is required to protect intellectual property rights, Investigator agrees to delay the disclosure for a period not to exceed an additional 60 days.

Investigator will, on request, remove any previously undisclosed Confidential Information (other than the Study results themselves) before disclosure.

If the Study is part of a multi-center study, Investigator agrees that the first publication is to be a joint publication covering all centers. However, if a joint manuscript has not been submitted for publication within 12 months of completion or termination of the Study at all participating sites, Investigator is free to publish separately, subject to the other requirements of this Section.

For all publications relating to the Study, Institution will comply with recognized ethical standards concerning publications and authorship, including Section II - "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index.html#authorship, established by the International Committee of Medical Journal Editors.

Publication of study results is also provided for in the Clinical Study Agreement between Pfizer and the institution. In this section entitled Publications by Investigators, the defined terms shall have the meanings given to them in the Clinical Study Agreement.

12. COMMUNICATION OF ISSUES

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable Competent Authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

In addition, the investigator will inform Pfizer immediately of any urgent safety measures taken by the investigator to protect the study patients against any immediate hazard, and of any serious breaches of this NI study protocol that the investigator becomes aware of.

13. REFERENCES

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14. LIST OF TABLES

None

15. LIST OF FIGURES

None

Appendix 1. LIST OF STAND ALONE DOCUMENTS

Number	Document reference number	Date	Title
1	Appendix A	In design	Patient/Caregiver Informed Consent Form
2	Appendix B	In design	Patient/Caregiver Questionnaire
3	Appendix C	In design	Physician CRF

Appendix 2. FACTOR USE BEHAVIOR QUESTIONS

In responding to this question, please think about what 'you did' / 'the child with hemophilia did' over the past month.

For the factor replacement therapy 'you use' / 'the child with hemophilia uses' to prevent and control bleeds, over the past month, how many times did 'you' / 'the child with hemophilia had to' **use an extra infusion for each of the following reasons?**

Felt pain which I thought was a bleed	Never	1 time	2 times	3 times	4 times or more
Bleeding episode	Never	1 time	2 times	3 times	4 times or more
Wanted additional protection before engaging in a sport or other impact activity	Never	1 time	2 times	3 times	4 times or more
Want extra protection for some another reason	Never	1 time	2 times	3 times	4 times or more
Other reason not listed	Never	1 time	2 times	3 times	4 times or more

Appendix 3. ENCePP checklist for study protocols

Not applicable

Appendix 4. ANNEX 4. Additional information

Not applicable