Non-Interventional Study Protocol
Haemophilia Treatment Patterns and Outcomes in Sweden
B1821054

Treatment Patterns and Outcomes in Patients Treated with BeneFIX or ReFacto/ReFacto AF – A Swedish Cohort Study

Statistical Analysis Plan
(SAP)

Version: 1

Author: PPD

Date: 3-November-2015

[redacted]

TABLE OF CONTENTS

[redacted]

1 AMENDMENTS FROM PREVIOUS VERSION(S)

This is the first version.

[redacted]

2 INTRODUCTION

In Sweden nearly 950 people suffer from bleeding disorders. Of these individuals, about 900 are diagnosed with haemophilia A (insufficient production of coagulation factor VIII) and B (insufficient production of coagulation factor IX). The distribution of patients with haemophilia A and B is about 80 percent and 20 percent respectively. About 50 people are diagnosed with von Willebrand disease [1]. All these patients lack sufficient levels of a protein in the blood that impacts the coagulation process. As a result the patients have a higher risk of having a bleed as well as suffer from prolonged bleeding. Bleeding can result in severe complications, especially in joints, and could result in permanent damage such as pain and disability [2].

Patients diagnosed with coagulation disorders receive intravenous replacement treatment of the missing coagulation factor. Replacement treatment can be given prophylactically, i.e., regularly to reduce the insufficiency to prevent bleeding to occur. It can also be given when a bleed occurs with the aim to stop the bleed and/or to stop it from becoming more severe, i.e., on demand treatment. The type of replacement treatment may depend on the severity of the disease [2].

At the Malmö Haemophilia Center (MHC) in Sweden patients diagnosed with bleeding disorders have been treated prophylactically since 1958. The treatment has intensified over time and today patients at the MHC, as well as Swedish patients in general, are treated from the age of 1-3 years [2]. Injections with replacement treatment for haemophilia A is generally given three to four times a week and for haemophilia B twice a week, when the disease is severe. The patients that belong to the MHC are well monitored - their treatments and outcomes have been registered in the Malmö Haemophilia Register (MHR) since 1977. The MHR therefore represents the best available source of information on treatments and outcomes of haemophilia in Sweden.

The first type of treatment available for Haemophilia A and B had a low percentage of coagulation factors and blood borne viruses such as Hepatitis C and HIV could be transferred to the patient. In the 1990's products that were produced using gene technology, recombinant products, with no risk of blood borne viruses, came to the market. Today several such products, among them ReFacto that was introduced in 1999 (ReFacto AF in 2009), exist for treatment of haemophilia A and most patients are treated with recombinant products [2, 3]. For treatment of haemophilia B four different replacement treatments exist and one of them (BeneFIX) is produced using gene technology [4]. In the US products with extended half-life, that make less frequent dosing

possible, are available. These products are expected to be available in the European market in the end of 2015/early 2016.

The aim of this study is to analyze the real world use of BeneFIX and ReFacto/ReFacto AF in haemophilia patients in Sweden. Sweden has a long tradition of population-based research within many therapeutic areas. Information in different registers can be record-linked by using the Swedish Personal Identification Number (PIN) that is unique to each Swedish citizen. The information available in the MHR linked together with information on treatments prescribed and picked up at the pharmacy, available in the Swedish prescription register, (held by the National Board of Health and Welfare, NBHW) provide a unique opportunity to provide in depth knowledge on actual treatment patterns and outcomes for patients diagnosed with haemophilia.

To our knowledge, no study to date has addressed in detail treatment outcomes, prescription patterns, actual treatment patterns, and the associated costs in a cohort of patients with coagulation disorders that are treated with BeneFIX or ReFacto/ReFacto AF. Previous research that has looked at treatment of haemophilia has e.g. focused on differences between the treatment regimens and the associated outcomes, see e.g. Berntorp et al (2012) for a review of such articles [5]. Recent research based on Swedish data investigates the long-term outcomes in haemophilia patients [6]. Previous research has also focused on real world treatment and outcomes in patients with inhibitors (see e.g. Osooli M et al (2015) for a systematic review of reasons for inhibitors and on what registries around the world have contributed to the learnings about inhibitors) [7-9]. Previous research has also focused on the HRQoL of haemophilia patients) [10].

2.1 STUDY DESIGN

The study will be carried out as a retrospective population-based register study. Detailed data or each patient diagnosed with haemophilia treated at the Skåne Univeristy Hospital (SUH) is collected in the MHR. The haemophilia patients treated at the SUH represent approximately 40 percent of the Swedish haemophilia population. The information in the MHR will be complemented with information from medical records. Information on drugs will be obtained from the Prescribed Drug Registry held by the NBHW. The information from the different sources will be record-linked at the MHC using the Swedish PINs that are unique to each Swedish citizen

The main strength of this study is that we are able to analyze the research questions in a population-based setting.

Study population

[redacted]

The study population will consist of all patients diagnosed with haemophilia (D66.9 (haemophilia A) D67.9 (haemophilia B) in International Statistical Classification of Diseases and Related Health Problems (ICD-10) that have been registered in the MHR since 1977 and that have had at least one registered prescription of BeneFIX or ReFacto/ReFacto AF in the MHR since market authorization of the respective product (Benefix August 27 1997, ReFacto April 13 1999, ReFacto AF July 1 2009). Diseased individuals are included. Information on drugs picked up at the pharmacy is available in the Prescribed Drug Register from2005.

The MHC is one of three haemophilia centers in Sweden and is responsible for treating about 40 percent of the Swedish haemophilia population.

Data source

Individual data will be extracted from the MHR and supplemented with information on surgery and/or bleed episodes from medical records when deemed necessary. Information on drugs prescribed and picked up from the pharmacy come from the prescribed drug register at the NBHW. The information from the different sources will be record-linked at the MHC by using the Swedish PINs that are unique to each Swedish citizen.

2.2 STUDY OBJECTIVES

This study is explorative, i.e., not hypothesis driven. The overall aim of the study is to describe demographic and clinical characteristics, treatment patterns and outcomes, as well as the related direct treatment costs in the populations of haemophilia patients treated with BeneFIX and ReFacto/ReFacto AF, and in subgroups (e.g. level of severity) at the MHC in Sweden.

In more detail the primary objectives are:

- *To describe basic demographic and clinical characteristics*
- *To describe prescription patterns, actual treatment patterns, and the relative dose intensity*
- *To describe treatment outcomes such as bleed and joint damage*
- *To study the relationship between bleed and actual treatment patterns*

[redacted]

- *To describe the use of replacement treatment administered in hospital in connection with invasive procedures*

The secondary objectives are:

- *To describe the costs associated with the prescription and actual treatment patterns*
- *To describe the costs associated with replacement treatment administered in hospitals*

3 INTERIM ANALYSES

N/A

4 HYPOTHESES AND DECISION RULES

N/A

4.1 STATISTICAL HYPOTHESES

N/A

4.2 STATISTICAL DECISION RULES

All data will be descriptive and standard statistical tests will be applied, see sections 6 and 8.

5 ANALYSIS POPULATION

5.1 THE MHR REFACTO/REFACTO AF BENEFIX POPULATION

The study population will consist of all patients diagnosed with haemophilia (D66.9 (haemophilia A) D67.9 (haemophilia B) in International Statistical Classification of Diseases and Related Health Problems (ICD-10) that have been registered in the MHR since 1977 and that have had at least one registered prescription of BeneFIX or ReFacto/ReFacto AF in the MHR since market authorization of the respective product (Benefix August 27 1997, ReFacto April 13 1999, ReFacto AF July 1 2009). Diseased individuals are included.

5.2 THE MHR REFACTO/REFACTO AF AND BENEFIX POPULATION - SUBGROUPS

Sub-group analyses of the MHR Refacto/Refacto AF and Benefix population will be carried out and results reported when the size of the group is at least five people.

The definition of sub-groups will be based on categorization in the MHR of

A. type of haemophlia, A and B;
B. severity of haemophilia according to standard classification, Mild, Moderate and Severe;
C. inhibitor status, Current, Ever and Never;
D. age groups, Children/Adolescents (0-17 years old) and Adults (18+ years old); and
E. period of analysis restricted to time periods when the patients are prescribed Refacto/Refacto AF or Benefix according to the MHR.

6 ENDPOINTS AND COVARIATES

6.1 BASIC DEMOGRAPHIC AND CLINICAL CHARACTERISTICS - DEFINITION OF VARIABLES AND DESCRIPTIVE ANALYSES

The variables that will be used to provide basic demographic and clinical characteristics of the MHR Refacto/Refacto AF and Benefix population are summarized in Table 1 below.

[redacted]

Table 1. Basic demographic and clinical characteristics as registered in the Malmö Haemophilia Register (MHR)

Characterization	**Variable**	**Descriptive statistics**	**Subgroup analysis*, see section 5.2 for subgroups**
Demographic characteristics	Year of birth	n, Min, Q1, Median, Q3, Max, Mean, SD	A, B, C
	Age group	n (%) child/adolescents and adults, respectively as defined by last available registration	A, B
	Sex	n(%) of men, women	-
	Deceased†	n(%) of deceased patients	A, B, C, D
Clinical characteristics	Type of bleeding disorder	n(%) of patients: Haemophilia A, haemophilia B	B, C, D
	Disease severity	n (%): Mild, Moderate, Severe	A, C, D
	Age at diagnosis	n, Min, Q1, Median, Q3, Max, Mean, SD	A, B
	Age at start of replacement treatment	n, Min, Q1, Median, Q3, Max, Mean, SD	A, B, C, D
	Age at start of treatment with Refacto/Benefix	n, Min, Q1, Median, Q3, Max, Mean, SD	A, B, C, D
	Inhibitor status†	n (%) by classification Current, ever, never inhibitors	A, B, D
	Hepatitis C antibody infected†	n (%) who has ever been infected by hepatitis C	A, B, C, D

[redacted]

	HIV positive†	n (%) with a positive HIV status	A, B, C, D

Notes: * results by sub-groups will be reported provided subgroups include at least 5 people. † The definition and derivation of the variable is further explained below.

For each variable the number and percentages of valid and missing observations are reported to provide an overview of data available for analysis.

Further description of derived variables marked with '†' presented in Table 1 above:

- *Deceased*: Date of death as recorded in the MHR. If no date of death is recorded, data is censored at August 31st, 2015.
- *Inhibitor status*: Based on last available observation in the MHR.
- *Hepatitis C antibody infected*: Based on last available observation in the MHR.
- *HIV positive*: Based on last available observation in the MHR.

6.2 TREATMENT CHARACTERISTICS - DEFINITION OF VARIABLES AND DESCRIPTIVE ANALYSES

A list of variables to describe and analyze treatment characteristics of patients in the MHR Refacto/Refacto AF and Benefix population is shown in Table 2 below. Treatment characteristics are presented as cross-sectional based on last available observation, development over time using annual observations, or as aggregated data over longer time frames. Descriptive analyses will use standard figures e.g. histograms and box plots as appropriate to summarize key information from the data set. See also section 6.4. The derivation of variables marked with an '†' is further elaborated below Table 2. Treatment characteristics data is sourced from the MHR and from the pharmaceutical register at the National Board of Health and Welfare (NBHW).

The severity of haemophilia is a key factor for determining the prescribed and actual replacement treatment strategy. The main descriptive analyses of treatment characteristics are therefore performed by standard classification of degree of severity as classified in the MHR. Subgroup analyses by type of haemophilia, inhibitor status, age-group and in the sample restricted to years when patients are prescribed Refacto/Refacto AF or Benefix will be performed by severity subgroups to reduce heterogeneity in expected replacement treatment strategy.

[redacted]

Table 2. Variables used to describing treatment characteristics based on information in the Malmö Haemophilia Register (MHR) and the pharmaceutical register at the National Board of Health and Welfare (NBHW). All analyses are conducted by subgroups of severity of haemophilia (Mild, Moderate and Severe) as defined in the MHR. Within those subgroups patients are divided into additional subgroups.

Characterization	**Variable**	**Descriptive statistics**	**Subgroup analysis*, see section 5.2 for subgroups**
Prescribed treatment Data from MHR	Prescribed dose per infusion†	• n, Min, Q1, Median, Q3, Max, Mean, SD Last available observation • Development over time	A, C, D, E
	Prescribed dose per kilogram body weight†	• n, Min, Q1, Median, Q3, Max, Mean, SD Last available observation • Development over time	A, C, D, E
	Prophylactic treatment	n(%) of patients on prescribed prophylaxis	A, C, D, E
	Prescribed frequency of infusion†	Per patient n, Min, Q1, Median, Q3, Max, Mean, SD	A, C, D, E
	Prescribed annual dose of factor concentrate	Per patient n, Min, Q1, Median, Q3, Max, Mean, SD	A, C, D, E

	Prescribed annual dose of factor concentrate per kilogram body weight†	Per patient n, Min, Q1, Median, Q3, Max, Mean, SD	A, C, D, E
	Annual registered consumption of factor concentrate†	Per patient n, Min, Q1, Median, Q3, Max, Mean, SD	A, C, D, E
	Type of factor concentrate	Number of patients by type of factor concentrate over time • Factor VIII concentrates • Factor IX concentrates • Factor rVIIa and/or aPCC	C
	Percentage of time on Refacto/Refacto AF and Benefix†	Per patient n, Min, Q1, Median, Q3, Max, Mean, SD	Total population
	Use of factor concentrates at hospital for invasive procedures †	n, Min, Q1, Median, Q3, Max, Mean, SD - Per event - Per patient per year - As percentage of total use of factor concentrate per patient per year	A, C, D, E

[redacted]

Filled prescriptions Data from NBHW Starting July 2005 the earliest.	Annual number of filled prescriptions of factor concentrate†	n, Min, Q1, Median, Q3, Max, Mean, SD of total number of filled prescriptions per patient. Data reported for last full calendar year and as development over time.	A, C, D, E
	Annual number of dispensed units†	n, Min, Q1, Median, Q3, Max, Mean, SD of total number of filled prescriptions per patient. Data reported for last full calendar year and as development over time.	A, C, D, E
	Percentage of units of Refacto/Refacto AF and Benefix†	n, Min, Q1, Median, Q3, Max, Mean, SD of total volume of units of Refacto/Refacto AF and Benefix as percentage of total volume of all factor VIII and IX concentrates, respectively, per patient.	Total population

Note: * results by sub-groups will be reported provided subgroups include at least 5 people. † The definition and derivation of the variable is further explained below.

Presentation of the descriptive analysis of treatment characteristics will consider the expected frequency of regular visits to the Malmö Haemophilia Center. Patients with severe haemophilia have regular and scheduled annual visits and this is the case also for many patients with moderate haemophilia. Patients with mild haemophilia are likely to have less frequent registrations and typically based on events increasing the risk of hemorrhages such as a planned or acute surgery. Analyses of the development over time of treatment characteristics are therefore expected to pertain primarily to patients with severe haemophilia and potentially also to patients with moderate haemophilia. Patients

[redacted]

with mild haemophilia as a group are expected to have few registrations over time for similar longitudinal analyses. Instead data on patients with mild haemophilia will be aggregated over longer time-spans such as 5- and 10 year periods.

The following general remarks apply to all analyses of longitudinal data:

- The standard longitudinal analysis will derive annual values based on calendar year (January 1 – December 31) and present these values by patient age.
- For patients with small irregularities in timing of annual visits, data may be re-allocated between to reflect one observation per calendar year.
- For patients with several registrations in a calendar year, e.g. young children, the mean of each year's observations will be calculated.

The list below elaborates further the derivation of variables marked with '†' in Table 2:

- *Dose per infusion*. The MHR contains registration of prescribed dose per infusion. Data is measured in international units (IU) for factor VIII and factor IX concentrates. Patients who develop inhibitors to factor VIII or IX concentrates may be treated with bypassing agents in the form of activated prothrombin complex concentrate (aPCC) which is measured in units (U) and/or recombinant factor VIIa (rFVIIa) measured in micrograms (µg).
- *Dose per kilogram body weight*. This is a set of two derived variables from the MHR based on information on prescribed replacement treatment:
    - prescribed dose per infusion divided by registered body weight (all patients); and
    - prescribed dose per week (prescribed dose per infusion multiplied by registered number of infusions per week) divided by registered body weight (only patients on prophylaxis).

  Results will be reported by type of replacement treatment (see description of *Dose per infusion* above).
- *Frequency of infusion*. The MHR allows registration of a multitude of individualized frequency of dosing regimens. These data will be reported in two ways. First, frequency of dosing are grouped into five categories:
    - daily or more often
    - every 2-3 day
    - every 3-4 day
    - every 5-7 day
    - when needed / episodic treatment

  Second, for patients on prophylaxis, the dosing regimen will be translated into *prescribed number of infusions per week*, a continuous variable with seven days

[redacted]

as base.

- *Prescribed annual dose of factor concentrate.* This variable is derived from the MHR registration of prescribed annual dose of factor concentrate
- *Prescribed annual dose of factor concentrate per kilogram body weight.* This variable is derived from the MHR registration of prescribed annual dose of factor concentrate and the registered body weight. Only relevant for patients on prophylaxis.
- *Annual registered consumption of factor concentrate*. The MHR contains registration of patient reports on factor concentrate consumption. The statistics will be reported including information on percentage of patients with complete self-reports and percentage of patients where no self-reports are available. Further analyses based on data on filled prescriptions on factor concentrates from the National Pharmaceutical Register will complement this information (see below)
- *Percentage of time on Refacto/Refacto AF and Benefix, respectively*. Derived variable calculated as total number of days when patient is prescribed Refacto/Refacto AF and Benefix over the total number of days on any replacement treatment. Total number of days on any replacement treatment is derived from date of start of replacement treatment according to MHR and August 31, 2015 or date of death, whichever is earliest.
- *Use of factor concentrates at hospital for invasive procedures.* Based on registration in MHR and clinical records. Information on year of surgery, type of surgery, type of factor concentrate and number of international units will be summarized for all years of observation. Descriptive statistics will be presented as totals and by type of surgery where at least five observations exist, as well as number of units per patient per year and as share of total use of factor concentrate per patient and year.
- *Annual number of filled prescriptions of factor concentrates*. Data from the NBHW contain information on all filled prescriptions from July 1, 2005 – last date of observation in the pharmaceutical register). These data will be annualized based on year in the variable dispense date.
- *Annual number of dispensed units*. To assess annual consumption of factor concentrates, calculations will define prescription date as start of use and the day before the next prescription as the last date of use of the factor concentrates retrieved. The annual number of dispensed units will then be the sum of all dispensed units with periods within the calendar year plus estimates of average daily use periods extending over two years. For example, a patient with two dispense dates on December 14, 2013 and January 25, 2014 in the NBHW, will have this filled prescription partitioned with factors 18/(18+24) on year 2013 and 24/(18+24) on year 2014.

[redacted]

- *Percentage of units of Refacto/Refacto AF and Benefix*. Data from the NBHW contain information on all filled prescriptions from July 1, 2005 – last date of observation (August 31, 2015). Derived variable calculated as total number of units of filled prescriptions of Refacto/Refacto AF and Benefix over the total units of all factor VIII concentrates and factor IX concentrates, respectively. Total number of units is derived from the date of start of NBHW to last available observation or date of death, whichever is earliest.

6.3 PATIENT OUTCOMES - DEFINITION OF VARIABLES AND DESCRIPTIVE ANALYSES

List of variables used to describe treatment characteristics of the MHR Refacto/Refacto AF and Benefix population is shown in Table 3 below. The derivation of variables marked with an '†' is further elaborated below Table 3.

[redacted]

Table 3. Variables for describing patient outcome variables as registered in the MHR. All analyses will be carried out by subgroups* of patients by type of haemophilia (A), severity of haemophilia (B), inhibitor status (C), age group (D) and in (E) the restricted sample containing the years when patients are prescribed Refacto/Refacto AF or Benefix according to the MHR.

Characterization	**Variable**	**Descriptive statistics**	**Subgroup analysis*, see section 5.2 for subgroups**
Treatment outcome	Total number of bleeds†	n, Min, Q1, Median, Q3, Max, Mean, SD of number of bleeds per patient per year	A, B, C, D, E
	Number of bleeds by type of bleed†	n, Min, Q1, Median, Q3, Max, Mean, SD of number of bleeds per patient per year and annualized per patient • Traumatic joint bleed • Spontaneous joint bleed • Traumatic bleed in soft tissue • Spontaneous bleed in soft tissue • Intracranical bleed • Gastrointestinal bleed • Urinary tract bleed	A, B, C, D, E
	Gilbert Joint Score†	n, Min, Q1, Median, Q3, Max, Mean, SD of score by last available registration and as development over time.	A, B, C, D, E
	Haemophilia Joint Health Score, HJHS†	n, Min, Q1, Median, Q3, Max, Mean, SD of score by last available registration and as	A, B, C, D, E

[redacted]

		development over time.	
	Surgery in joint for haemophilia related problems†	Total number of surgeries by type of surgery. Number of patients who have conducted one, two or three or more, respectively, joint surgeries.	A, B, C, D, E

Note: * results by sub-groups will be reported provided subgroups include at least 5 people. † The definition and derivation of the variable is further explained below.

Further elaboration of the derivation of the selection of variables marked with '†':

- *Total number of bleeds*. The total number of bleeds per patient per year is summarized and reported to provide an overview of the number of events per year without reference to the severity.
- *Number of bleeds by type of bleed*. The total number of bleeds per type per patient per year is summarized and reported to provide an overview of the number of events per year without reference to the severity.
- *Gilbert Joint Score*. Data available until 2008/2009. Thereafter the MHR use the HJHS (see below).
- *Haemophilia Joint Health Score, HJHS*. Data available from 2008/2009. Joint health was recorded using the Gilbert score prior to 2008/2009 (see above).
- *Surgery in joint for haemophilia related problems*. Based on registration in MHR and clinical records on year of surgery and type of surgery. Descriptive data will be presented as
    - total number of invasive procedures by type;
    - number of patients who have conducted one, two or three or more, respectively, joint surgeries.

6.4 COMPARATIVE ANALYSIS OF PRESCRIBED AND DISPENSED ANNUAL FACTOR CONCENTRATE VOLUMES

A comparative analysis will be carried out comparing prescribed drug and the actual use of drug measured with two variables; the annual registered consumption of factor concentrate and the annual dispensed volume of factor concentrate.

The analysis will focus on two variables that measure the relative dose intensity:

[redacted]

- Relative dose intensity based on patient registered volume of units consumed. This is a derived variable using annual registered consumption of factor concentrate per patient divided by annual prescribed dose per patient.
- Relative dose intensity based on dispensed volume of units. This is a derived variable using annual dispensed volume of factor concentrate per patient divided by annual prescribed dose per patient.

These variables will be described using the following statistical measures; n, Min, Q1, Median, Q3, Max, Mean, SD.

In addition a graphical analysis will be conducted using prescribed annual replacement treatment based on MHR registration and consumed volumes (based on MHR registration and dispensed volumes of replacement treatment (as recorded in the NBHW). The graphical analysis uses all annual observations for each patient and scatterplots consumed and dispensed volumes against prescribed volumes.

The comparative analyses will be conducted for patients prescribed prophylaxis according to MHR. Within this group the subgroups type of haemophilia (A), severity of haemophilia (B), age group (D) and the restricted sample containing the years when patients are prescribed Refacto/Refacto AF or Benefix according to the MHR (E) will be investigated separately for groups of at least 5 patients.

6.5 ANALYSIS OF COSTS

Analysis of costs associated with prescription and actual treatment patterns will be based on pharmacy retail prices from the pharmaceutical register at the National Board of Health and Welfare (AUP). Costs will be presented in SEK and adjusted for inflation. Cost outcome variables are presented below in Table 4.

[redacted]

Table 4. Cost outcomes variables based on information in the MHR and pharmacy retail prices from the pharmaceutical register at the National Board of Health and Welfare. All analyses are conducted by subgroups of severity of haemophilia (Mild, Moderate and Severe) as defined in the MHR. Within those subgroups patients are divided into additional subgroups.

Characterization	**Variable**	**Descriptive statistics**	**Subgroup analysis*, see section 5.2 for subgroups**
Costs	Annual total cost (SEK) of prescribed factor concentrates†	n, Min, Q1, Median, Q3, Max, Mean, SD of annual cost of total prescribed factor concentrate per patient based on MHR data	A, C, D
	Annual total cost (SEK) of dispensed replacement treatment†	n, Min, Q1, Median, Q3, Max, Mean, SD of annual total cost of dispensed factor concentrates per patient based on NBHW data	A, C, D
	Cost (SEK) of replacement treatment related to bleeds	n, Min, Q1, Median, Q3, Max, Mean, SD of costs of replacement treatment for bleeds in MHR. – Cost per bleed event – Annual cost of replacement treatment related to bleeds total and per patient – As percentage of total annual cost for use of replacement treatment, total and per patient	A, C, D

[redacted]

	Cost (SEK) of replacement treatment administered in hospitals for joint surgery	n, Min, Q1, Median, Q3, Max, Mean, SD of costs of replacement treatment administered in hospital for joint surgery based on data in MHR. - Cost per event - Annual cost of replacement treatment related to joint surgery total and per patient - As percentage of total annual cost for use of replacement treatment, total and per patient	A, C, D
	Cost (SEK) of replacement treatment administered in hospital for invasive procedures	n, Min, Q1, Median, Q3, Max, Mean, SD of costs of replacement treatment administered in hospital for invasive procedures based on data in MHR. - Cost per event - Annual cost of replacement treatment related to invasive procedures, total and per patient - As percentage of total annual cost for use of replacement treatment, total and per patient	A, C, D

[redacted]

Note: * results by sub-groups will be reported provided subgroups include at least 5 people. † The definition and derivation of the variable is further explained below.

- *Annual total cost of prescribed factor concentrates*: Median, range, interquartile range of annual cost of total prescribed factor concentrate per patient based on MHR data. The costs of prescribed factor concentrates will be derived based on data on volumes from the MHR and on prices of factor concentrates from 2015 available from the NBHW.
- *Annual total cost of dispensed replacement treatment*: Based on filled prescriptions in NBHW, number of dispensed units and the registered retail price (AUP).
- *Cost of replacement treatment related to bleeds*: Median, range, interquartile range of costs of replacement treatment for bleeds in MHR. The costs of factor concentrates used for treating bleeds will be derived based on data on volumes from the MHR and on prices of factor concentrates from 2015 available from the NBHW.
- *Cost of replacement treatment administered in hospitals for joint surgery*: Median, range, interquartile range of costs of replacement treatment administered in hospital for joint surgery based on data in MHR. The costs of factor concentrates used for treating for surgery will be derived based on data on volumes from the MHR and on prices of factor concentrates from 2015 available from the NBHW.
- *Cost of replacement treatment administered in hospitals for invasive procedures*: Median, range, interquartile range of costs of replacement treatment administered in hospital for invasive procedures based on data in MHR. The costs of factor concentrates used for treating for surgery will be derived based on data on volumes from the MHR and on prices of factor concentrates from 2015 available from the NBHW.

7 HANDLING OF MISSING VALUES

Missing values can be expected for the self-reported bleeds and consumption of factor concentrate. Values for the Gilbert and the HJHS scores may also be missing due to non-reporting into the register. Missing values will be handled in the following ways.

- Patient reported factor concentrate consumption: Missing values will handled in two different ways 1) missing values will be replaced by imputation using average

[redacted]

consumption from reported months during calendar year 2) it will be assumed that non reporting of consumption means that there was no consumption.
- Gilbert and HJHS scores: As a sensitivity analysis results will be presented based on linear approximation, when possible, otherwise last value carried forward.
- Lack of reporting on bleeds cannot be adjusted for.

8 STATISTICAL METHODOLOGY AND STATISTICAL ANALYSES

8.1 STATISTICAL METHODS

The data material is expected to exhibit non-symmetric (skewed) distributions and the main strategy for all descriptive analyses of all continuous variables is to present non-parametric analyses including median, range and interquartile range including values of first and third quartile. Complementary analyses assuming symmetric distributions including mean and standard deviation may be presented for comparison. Categorical data will be presented as frequency and proportions (using percentages). These strategies will apply to subgroup analyses as well.

The longitudinal structure of the data enables estimation of correlations between variables with better precision as data contain several observations per individual. Panel data regression methods [11] will be applied to explore to what extent the annual use of factor concentrate can be explained by individual characteristics including age, residual body weight, prescribed dose per infusion and/or deviation from average recommended dose per kg body weight. Estimations may be carried out in the full sample and in subsamples excluding persons with current or previous inhibitor status, an in the subsample containing only people with complete monthly reports. Panel data regressions may also be used to explore potential correlations between having had at least one haemorrhagic episode and age, residual body weight, prescribed dose per infusion and/or deviation from average recommended dose per kg body weight. Potentially, count data panel regression models may be used to explore correlations to the number of bleeds. However, patients with prophylaxis may be expected to bleed rarely and not more than once a year and many not at all [11]. The variable annual bleed rate is expected to be skewed and also to contain a large number of people with zero observations.

The statistical analyses will be carried out using Stata/IC 13.1 for Windows, or later versions of this programme.

[redacted]

8.2 STATISTICAL ANALYSES

Analysis of primary outcomes variables

Demographic variables:

- Year of birth
- Age group (see Table 1)
- Sex
- Deceased

Clinical characteristics:

- Type of bleeding disorder
- Disease severity
- Age at diagnosis
- Age at start of replacement treatment
- Age at start of treatment with Benefix/Refacto
- Inhibitor status
- Hepatitis C antibody infected
- HIV positive

Treatment characteristics:

- Prescribed dose per infusion
- Prescribed dose per kilogram body weight
- Prophylactic treatment
- Prescribed frequency of infusion
- Prescribed annual dose of factor concentrate
- Prescribed annual dose of factor concentrate per kilogram body weight
- Annual registered consumption of factor concentrate
- Type of factor concentrate
- Percentage of time on Refacto/Refacto AF and Benefix
- Use of factor concentrates at hospital for invasive procedures
- Annual number of filled prescriptions of factor concentrates
- Annual number of dispensed units
- Percentage of units of Refacto/Refacto AF and Benefix

Treatment outcomes:

- Total number of bleeds
- Number of bleeds by type of bleed
- Gilbert Joint Score
- Haemophilia Joint Health Score, HJHS
- Surgery in joint for haemophilia related problems

Comparative dosing analysis:

- Relative dose intensity based on patient registered consumption

[redacted]

- Relative dose intensity based on dispensed volume of units
- Graphical analysis plotting prescribed volume for each patient and year against registered consumption and dispensed consumption

Analysis of secondary outcomes variables

- Annual total cost in SEK of prescribed factor concentrates
- Annual total cost in SEK of dispensed replacement treatment
- Cost of replacement treatment related to bleeds (in SEK)
- Cost of replacement treatment administered in hospitals for joint surgery (in SEK)
- Cost of replacement treatment administered in hospital for invasive procedures (in SEK)

Costs will be presented in SEK and adjusted for inflation using year 2014 as the base year.

Further details on descriptive statistics by variable are found in Tables 1 through 4 in Sections 6.1 – 6.5.

8.2.1 Safety Analyses

N/A

8.2.2 Summary of Analyses

Analyses, tables and illustrations will follow the structure described in section 6.

9 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study uses existing health care databases, in which it is generally not possible to link (i.e. identify a potential association between) a particular product and medical event for any individual. In addition, this study protocol requires human review of patient-level unstructured data; unstructured data refer to verbatim medical data, including text-based descriptions and visual depictions of medical information, such as medical records, images of physician notes, neurological scans, X-rays, or narrative fields in a database. The reviewer is obligated to report adverse events (AE) with explicit attribution to any Pfizer drug that appear in the reviewed information (defined per the patient population

and study period specified in the protocol). Explicit attribution is not inferred by a temporal relationship between drug administration and an AE, but must be based on a definite statement of causality by a healthcare provider linking drug administration to the AE.

The requirements for reporting safety events on the non-interventional study (NIS) adverse event monitoring (AEM) Report Form to Pfizer Safety are as follows:

- All serious and non-serious AEs with explicit attribution to any Pfizer drug that appear in the reviewed information must be recorded on the chart abstraction form and reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form

- Scenarios involving drug exposure, including exposure during pregnancy, exposure during breast feeding, medication error, overdose, misuse, extravasation, lack of efficacy and occupational exposure associated with the use of a Pfizer product must be reported, within 24 hours of awareness, to Pfizer Safety using the NIS AEM Report Form.

For these safety events with an explicit attribution to or associated with use of, respectively, a Pfizer product, the data captured in the medical record will constitute all clinical information known regarding these adverse events. No follow-up on related adverse events will be conducted.

All research staff members 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 will be provided to all research staff members prior to study start. 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.

10 LIST OF TABLES AND TABLE SHELLS

Table 1. Basic demographic and clinical characteristics as registered in the Malmö Haemophilia Register (MHR)

Table 2. Variables used to describing treatment characteristics based on information in the Malmö Haemophilia Register (MHR) and the pharmaceutical register at the National Board of Health and Welfare (NBHW)

Table 3. Variables for describing patient outcome variables as registered in the MHR

Table 4. Cost outcomes variables based on information in the MHR and pharmacy retail prices from the pharmaceutical register at the National Board of Health and Welfare

11 REFERENCES

1. Socialstyrelsen, *Blödarsjuka* i serien Ovanliga diagnoser; 2011

2. Svenska riktlinjer för behandling av blödarsjuka, Hemofilicentra i Malmö, Göteborg och Stockholm, Förbundet blödarsjuka i Sverige; 2003

3. European Medicines Agency, European Public Assessment Report for ReFacto (Accessed April 27, 2015)

4. European Medicines Agency, European Public Assessment Report for BeneFIX (accessed April 27, 2015)

5. Berntorp, E., Astermark, J., Baghaei, F., Bergqvist, D., Holmström, M., Ljungberg, B., Norlund, A., Palmblad, J., Petrini, P., Stigendal, L. and Säwe, J. (2012), Treatment of haemophilia A and B and von Willebrand's disease: summary and conclusions of a systematic review as part of a Swedish health-technology assessment. Haemophilia, 18: 158–165. doi: 10.1111/j.1365-2516.2011.02723.x

6. Lövdahl S, Henriksson KM, Baghaei F, Holmström M, Nilsson JÅ, Berntorp E, Astermark J. Incidence, mortality rates and causes of deaths in haemophilia patients in Sweden. Haemophilia. 2013 May;19(3):362-9.

7. Osooli M*,* Berntorp E *(Skåne University Hospital, Lund University, Malmö, Sweden)*. Inhibitors in haemophilia: what have we learned from registries? A systematic review (Review). J Intern Med 2015*;* 277*:* 1–15.

8. Chambost, H., Santagostino, E., Laffan, M., Kavakli, K. and The ONE Registry Steering Committee on behalf of the investigators (2013), Real-world outcomes

[redacted]

with recombinant factor VIIa treatment of acute bleeds in haemophilia patients with inhibitors: results from the international ONE registry. Haemophilia, 19: 571–577. doi: 10.1111/hae.12140

9. Shapiro, A. D., Neufeld, E. J., Blanchette, V., Salaj, P., Gut, R. Z. and Cooper, D. L. (2014), Safety of recombinant activated factor VII (rFVIIa) in patients with congenital haemophilia with inhibitors: overall rFVIIa exposure and intervals following high (>240 μg kg^{-1}) rFVIIa doses across clinical trials and registries. Haemophilia, 20: e23–e31. doi: 10.1111/hae.12329

10. Lindvall, K., Von Mackensen, S. and Berntorp, E. (2012), Quality of life in adult patients with haemophilia – a single centre experience from Sweden. Haemophilia, 18: 527–531. doi: 10.1111/j.1365-2516.2012.02765.x

11. Jones, A.M., et al., Applied Health Economics, Second Edition. 2013: Routledge.Angrist, J.D. and J.-S. Pischke, Mostly harmless econometrics. An empiricist's companion. 2009: Princeton University Press.

[redacted]

12 APPENDICES

NA

12.1 APPENDIX 1: DATA DERIVATION DETAILS

NA

A1.2 Further definition of endpoints

12.2 APPENDIX 2: ADDITIONAL STATISTICAL METHODOLOGY DETAILS

NA

A2.1 Further Details of the Statistical Methods

NA

[redacted]