Official Title: A Multicenter, Non-Interventional Study to Evaluate Physical Activity, Bleeding Incidence and Health Related Quality of Life, in Patients With Haemophilia A Without Inhibitors Receiving Standard Of Care Treatment

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NIS PROTOCOL (PRIMARY DATA COLLECTION)

TITLE:	A multicenter, non-interventional study to evaluate physical activity, bleeding incidence and health related quality of life, in patients with haemophilia A without inhibitors receiving standard of care treatment
PROTOCOL NUMBER:	ML40983
VERSION NUMBER:	3.0
STUDIED MEDICINAL PRODUCT:	None
INDICATION:	Haemophilia A without inhibitors
STUDY INITIATOR:	Roche S.p.A. Viale G.B. Stucchi,110 20900 MONZA, MB (Italy)
AUTHOR:	[redacted]
DATE FINAL:	26 Jul 2019

FINAL PROTOCOL APPROVAL

Date and Time (UTC)	Title	Approver's Name
31-Jul-2019 12:02:49	Company Signatory	[redacted]

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PROTOCOL ACCEPTANCE FORM

TITLE:	A multicenter, non-interventional study to evaluate physical activity, bleeding incidence and health related quality of life, in patients with haemophilia A without inhibitors receiving standard of care treatment
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I agree to conduct the non-interventional study in accordance with the current protocol.

_____

Treating Physician's Name (print)

_____ _____

Treating Physician's Signature Date

Please return a copy of this form to the contact provided below. Please retain the signed original for your study files.

Medical Affairs & Clinical Operations, Roche SpA, Viale G.B. Stucchi 110, 20900 Monza (MB) to the kind attention of Country Head of Clinical Operations

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
ABR	Annualised Bleeding Rate
AE	Adverse Event
AICE	Italian Association of Hemophilia Centres
BMI	Body Mass Index
BYOD	Bring Your Own Device
CD	Compact Disc
CFR	Code of Federal Regulations
CI	Confidence Interval
CRA	Clinical Research Associate
CRO	Contract Research Organization
DVD	Digital Video Disc
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
ePRO	Electronic Patient-Reported Outcome
EQ-5D-5L	European Quality of Life-5 Dimensions
ETV	Early Termination Visit
EU	European Union
FVIII	Factor VIII
GPP	Good Pharmacoepidemiological Practice
GVP	Good Pharmacovigilance Practice
HJHS	Haemophilia Joint Health Score
HRQoL	Health-Related Quality Of Life

ICH	International Conference on Harmonization
INPS	Istituto Nazionale della Previdenza Sociale
ISPE	International Society of Pharmacoepidemiology
MET	Metabolic Equivalent of Tasks
NIS	Non Interventional Study
NSAIDs	Non-steroidal Anti-inflammatory Drugs
PDF	Portable Document Format
PT	Preferred Term
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Statistical Analysis Software
SDV	Source Data Verification
SOC	System Organ Class
ULN	Upper Limit of Normal
VAS	Visual Analogue Scale
WHO	World Health Organization

2. SYNOPSIS

TITLE:	A multicenter, non-interventional study to evaluate physical activity, bleeding incidence and health related quality of life, in patients with haemophilia A without inhibitors receiving standard of care treatment
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STUDIED INITIATOR:	Roche S.p.A. Viale G.B. Stucchi,110 20900 MONZA, MB (Italy)
MAIN AUTHOR:	[redacted]

Research Question and Objectives

Objectives

The primary objective for this study is to document physical activity, particularly in terms of active minutes, steps count and Metabolic Equivalent of Tasks (MET) over the 12 months period, by age categories (12-17, 18-30 and 31-50 years) in patients with haemophilia A without inhibitors receiving standard of care treatment.

The secondary objectives for this study are as follows:

- To document physical activity, particularly in terms of active minutes, by ages categories (12-17, 18-30 and 31-50 years), by type of physical activity and by intensity (as per fitness tracker default categorization);
- To describe the observed population in terms of:
  - Number of patients who are adherent to World Health Organization (WHO) Guidelines (*i.e.*, Global Recommendations on Physical Activity for Health) for the definition of physical activity;
  - Number and type of bleeds occurring during routine clinical practice and reported at any occurrence via the electronic Patient-Reported Outcome (ePRO) application;
  - Treatment regimen for haemophilia A (prophylaxis, preventative treatment before physical activity, treatment for any episode of bleeds), in terms of type of regimen (on-demand vs. prophylaxis), product used and dose;
  - Health-Related Quality of Life (HRQoL) and health status (evaluated at baseline, every three months, and at the end of the study) reported during routine clinical practice, measured using the European Quality of Life-5 Dimensions (EQ-5D-5L) score (adults/adolescents);
  - Dose and frequency of concomitant medications taken to control pain (*e.g.*, nonsteroidal anti-inflammatory drugs [NSAIDs], painkillers);

- Joint health status of enrolled patients, based on Haemophilia Joint Health Score (HJHS) questionnaire (evaluated at baseline, at six months, and at the end of the study);
- Body Mass Index (BMI) evaluated at baseline and every three months;
- Number of days away from school (patient) and/or work (patient and caregiver), and age of possible early retirement (caregiver) during the observation period, evaluated through administration of questions (evaluated at baseline, every month, and at the end of the study);
- Number of hospitalization days (patient) during the observation period evaluated through administration of questions (evaluated at baseline, every month, at the end of the study);
- Pain intensity measured using a Visual Analogue Scale (VAS) (evaluated at baseline, every month, and at the end of the study);

• To evaluate adherence to the treatment regimen:
  - Documented during planned visits according to source data (ePRO data) in electronic Case Report Forms (eCRF) by the Investigator;
• To describe the active vs. sedentary haemophiliac patients in terms of:
  - Severity of disease;
  - Annualized Bleeding Rate (ABR);
  - Pain and use of painkillers;
  - Drug regimen adopted;
  - HRQoL;
  - Hospitalization/missed days at school; - Joint Health Status.
• To describe severe vs. moderate haemophiliac patients for the above mentioned items.

Exploratory Objectives

The exploratory objectives for this study are as follows:

• To evaluate the relationship between physical activity (type and intensity) and bleedings;
• To evaluate the sleep duration and sleep stage in participant patients;
• To observe patients, on primary and secondary objectives, for additional 6 months if new therapies become commercially available for patients with Haemophilia A without inhibitors against FVIII, during the course of the study and if patient will start such treatments during the observation period

  In the context of this study, newly approved drugs are considered all those newly approved during the course of the study and commercially available for prophylaxis treatment in patients with haemophilia A without inhibitors (See section 4.1).

Study Design

This is a multicenter, non-interventional, prospective study. The study will be conducted according to the following scheme:

	Observational period	
	Standard observational period for all observed patients	Month 0 to Month 12

Baseline	**Prolonged observational period If patients start newly approved drugs between Month 6 and Month 12**	6 Months after the start of new therapy (*e.g.*, max observation period of 18 months if patients start the newly approved drugs during the last month of standard observational period)

This study will include patients aged ≥ 12 years and ≤ 50 years with severe (FVIII < 1%) or moderate (FVIII ≥ 1 and ≤ 2%, i.e. in the higher range of severity) Haemophilia A without inhibitors against FVIII receiving standard of care treatment. During the study, HRQoL, health status and joint health status will be reported on a pre-determined frequency for 12-18 months, as shown in the Data Collection Overview (Appendix 2). Physical activity data will be collected daily using a fitness tracker.

Approximately 150 patients overall, 125 patients with severe haemophilia A and 25 patients with moderate haemophilia A without inhibitors against FVIII are planned to be enrolled.

Additionally, patients (or patient's legally authorized representative) will be reminded on a monthly basis to report via the ePRO application whether a bleed has occurred and whether treatment for a bleed or treatment to prevent a further bleed has been given. When a bleed occurs, the patient (or patient's legally authorized representative) will be required to report bleed information, including site of bleed, type of bleed, time of each individual bleed (date, time of start and time of end), symptoms of bleed, and treatment for bleed.

Physical activity will be measured daily by wearing a fitness tracker continuously during study participation. Patients will be reminded to wear the device daily. A valid day of monitoring is defined as at least 10 wear hours per day. Wear time will be derived through data collected by the fitness tracker.

The reason for the use of coagulation products will be documented by Investigator in source data and reported in the eCRF (*e.g.*, bleeding, prophylaxis, pain, etc.). The reason for the use of coagulation products for bleeding treatment, including agent, start time, dose, route of administration, and number of infusions needed to treat the bleed, will be recorded by patients in the ePRO application and will be then transmitted to the eCRF.

Therapy will be recorded by the investigator at baseline visit and it will afterwards be confirmed by the patient in ePRO application. If there are changes to the assigned therapy, the patient will enter therapy variations in ePRO (*e.g.*, dose, frequency, drug name etc.) and data will be then transmitted to the eCRF.

Demographics and results from physical examinations, and vital sign assessments, will only be collected if available from routine clinical practice. No additional diagnostic or monitoring procedures will be applied to the patients outside of routine clinical practice.

The usage of ePROs is considered non-interventional according to local regulation.

Start Date of Study:

The study start date will be the date of the signing of informed consent of the first patient (or caregiver). The planned start date is October 2019.

End of Study

The end of the study will be the date on which the last patient performs the last visit. This is expected when:

- The last patient completes the 12-month observation period (and patients that start treatment with any newly approved drugs between Month 6 and Month 12 complete a 6 months observational period after the start of therapy), or
- The last patient has lost to follow up, withdraws consent or died whichever occurs first, or
- The study has been terminated by the Sponsor, if earlier.

Length of Study

This study will last approximately 24 months (approximately 6 months for enrolment, 12 months of observational period and up to 6 months of observation for patients that will start treatment with any newly approved drugs between Month 6 and Month 12).

Patients that will start treatment with any newly approved drugs between Month 6 and Month 12 will complete a 6-month observational period after the start of therapy, and therefore the entire observational period in these patients may be prolonged up to a maximum of 18 months. Visits at the clinic will be performed according to Investigator's judgment and local clinical practice: it is estimated that visits will take place approximately every three months, with some degree of flexibility (*e.g.*, ± 1 month or higher) according to local standard of care.

Target Population

Patients aged ≥12 years and ≤ 50 years with severe or moderate haemophilia A without inhibitors against FVIII receiving standard of care treatment.

Patients must meet the following criteria for study entry:

1. Signed informed consent
   - Consent/assent will be taken as appropriate from patient, parent or legal guardian, according to age and applicable regulations.
2. Must own a device compatible with the ePRO application and with the fitness tracker that will be provided to the patient (Fitbit Versa model); please refer to appendix 6 for an exhaustive list of acceptable devices.
3. Must have on his/her own device a data traffic availability of at least 2 GB in total per month intended only for use of study applications and data transfer. If the data traffic plan is exhausted, the patient must be able to connect to a wi-fi network at least once every day in order to transfer the data collected for the study purpose.
4. Must accept to run on his/her own device the ePRO application and the fitness tracker application.
5. Must be available to turned on daily the bluetooth connection of his/her own device in order to allow the synchronization with the fitness tracker.
6. Ability and willingness to comply with all aspects of the protocol, including completion of questions on the ePRO application (for underage population, ePRO questions can be answered by legally authorized representative if deemed necessary).
7. Ability and willingness to wear the activity tracking device as indicated.
8. Patients aged ≥12 years and ≤ 50 years at time of informed consent.
9. Diagnosis of severe (FVIII < 1%) or moderate (FVIII ≥ 1 and ≤ 2%) congenital haemophilia A.

10. No prior history of a positive inhibitor against FVIII. If patient has a previous history of inhibitor development, the patient must have successfully eradicated inhibitors since 3 years.
11. At least 150 exposure days of FVIII prior to enrolment.

Patients who meet any of the following criteria will be excluded from study entry:

1. Bleeding disorder other than congenital haemophilia A.
2. Ongoing (or planned during the study) immune tolerance induction or FVIII prophylaxis if the patient has currently low title of inhibitors or had inhibitors in the past three years
3. Previous or concomitant autoimmune or connective tissue disease.
4. History of or suspected allergy or intolerance to any of the component of the fitness device (*e.g.*, aluminium anodised).
5. History of clinically significant hypersensitivity associated with monoclonal antibody
6. Obesity (BMI ≥ 30 kg/m^2).
7. Clinically important cardiovascular, metabolic, endocrine disorders or any other concomitant diseases or conditions that could limit the mobility of patients or could represent any risk according to the Investigator's judgment, or that could interfere with the study evaluation parameters.
8. Participation in any other interventional clinical trial, including Roche sponsored studies, or in any other support program that may include drug administration other than standard clinical practice (*e.g.*, compassionate use, use not in agreement with the authorized indications, patient support programs, etc.).

Variables

Only data obtained during routine clinical practice and in compliance with the study objectives will be documented in this study.

Primary Variable

The primary variable for this study is:

• Physical activity data collected through a wearable device (*i.e.*, fitness tracker) in terms of active minutes, METs and step counts.

Secondary Variables

The secondary variables for this study are:

- Adherence to WHO Guidelines for the definition of physical activity;
- Date and time of bleed start and end;
- Sites of bleed;
- Types of bleed (spontaneous, traumatic);
- Treatment for bleed (episodic or prophylaxis agent and/ or other agent used, dose, route, start date and time of treatment used);
- Treatment regimen for Haemophilia A (episodic, prophylaxis, preventative treatment before physical activity), in terms of type of regimen (on-demand vs. prophylaxis), product used and dose, and adherence to treatment regimen;
- HRQoL through EQ-5D-5L and health status;

- Dose and frequency of concomitant medications taken to control pain (*e.g.*, NSAIDs, painkillers);
- Joint health status based on HJHS questionnaire;
- BMI;
- Number of days away from school (patient) and/or work (patient and caregiver), and age of possible early retirement (caregiver) during the observation period;
- Number of hospitalization days (patients) during the observation period;
- Pain intensity measured using a VAS;
- Engagement in physical activity (i.e. Active/Sedentary);
- Severity of disease.

Other Variables of Interest

- Newly approved drugs, if patients will start such therapies during the observation period;
- Sleep duration and stages collected through a wearable device (i.e., fitness tracker).

All data will be recorded on eCRFs. The degree of detail and completeness of data collected will be dependent on local clinical practice. Data from source documents should be entered on the eCRF as soon as they become available. Daily physical activity data will be collected continuously via the wearable device (*i.e.*, fitness tracker). HRQoL, VAS for pain, missed days at school (patient) and/or work (patient and caregiver), age of possible early retirement (caregiver), number of hospitalization days (patients), bleeding information and drugs administered to treat Haemophilia (treatment for bleeds, episodic or prophylactic treatments, preventative treatment before physical activity) will be recorded by the patient through ePRO application according to protocol requirements (refer to Appendix 2, Data Collection).

Data Source

All data will be recorded on electronic case report forms (eCRFs). The degree of detail and completeness of data collected will be dependent on local clinical practice. Data from source documents should be entered on the eCRF as soon as they become available. Daily physical activity data will be collected continuously via the wearable device (*i.e.*, fitness tracker). HRQoL, VAS for pain, missed days at school (patient) and/or work (patient andcaregiver), age of possible early retirement (caregiver), number of hospitalization days (patients), bleeding information and drugs administered to treat Haemophilia (treatment for bleeds, episodic or prophylactic treatments, and preventative treatment before physical activity) will be recorded by the patient through ePRO application according to protocol requirements (refer to Appendix 2, Data Collection).

Data Analysis

The appointed Contract Research Organization (CRO) will be responsible for the statistical analysis of the study.

All statistical analyses and data processing will be performed using The Statistical Analysis Software (SAS), release 9.4 or later, under Windows 7 or Windows 10 Pro operating system.

The statistical methods planned in this study protocol (see below) will be detailed, agreed and approved in a statistical analysis plan (SAP) which will be finalized before database lock.

One interim analysis is planned, when all enrolled patients have completed 6 months of observation. Details of this analysis will be provided in the SAP.

Descriptive statistics will be provided in summary tables according to the type of the variable. Continuous variables will be summarized by using number of cases, mean, and standard deviation, median, quartiles and range (i.e. minimum and maximum). Categorical variables will be summarized by using frequency and percent distribution.

Primary variables (*i.e.*, daily evaluations of active minutes, step counts and METs) will be analyzed over the 12 months' observational period by means of descriptive statistics (e.g. weekly/monthly). The 95% confidence interval (CI) of the mean will be also presented. Moreover, results will be also shown graphically, if deemed necessary.

Analyses on primary variables will be conducted on patients with established valid measurements from the fitness tracker.

A sensitivity analysis could also be performed evaluating the relationship of primary variables with baseline, demographic or other clinically relevant variables which will be detailed and described in the SAP.

Secondary variables will be summarized by using descriptive statistics as indicated in general methodology section, according to the type of variable analyzed, at any given time point (where applicable). The 95% CI of the mean change could be also presented.

Particularly, the proportion of patients who will meet WHO recommendations for physical activity will be summarized using descriptive statistics and 95% CIs as well.

The same analysis will be performed on active/sedentary patients and severe/moderate patients.

A further exploratory analysis will be performed in patients that will start treatment with any newly approved drugs during the study. An intra-patients comparison will be performed on pre and post treatment start primary and secondary variables evaluations, through means of descriptive statistics.

Due to the exploratory nature of this study, no adjustment for multiplicity will be made.

Study Size/Determination of Sample Size

Given the exploratory nature and the objectives of this non-interventional study, rather than testing a formal hypothesis, a justification based on epidemiologic data from the Italian registry of congenital bleeding disorders (*Giampaolo et al. 2017*) was considered more appropriate than a power calculation in the traditional fashion or using an estimation approach through the precision of confidence intervals.

Based on data collected from the 54 Hemophilia Treatment Centers, members of the Italian Association of Hemophilia Centres (AICE), it is estimated that the planned number of participants in this study will represent approximately 10-15% of patients with Haemophilia A in Italy in the same age range and category of severity planned for this study. The total sample size planned is approximately 150 patients overall, 125 patients with severe Haemophilia A and 25 patients with moderate Haemophilia A.

3. PROTOCOL AMENDMENTS AND UPDATES

Any protocol amendments will be prepared by study initiator.

Protocol amendments will be submitted to the Ethics Committee (EC) and to regulatory authorities in accordance with local regulatory requirements.

Approval must be obtained from the EC and regulatory authorities (as locally required) before implementation of any changes, except for changes that involve logistical or administrative aspects only (*e.g.*, change in Site Operations Representative or contact information).

Substantial protocol amendments/updates so far: none.

4. RATIONALE AND BACKGROUND

Haemophilia A is an X-linked recessive bleeding disorder that occurs in approximately 1 in 5000 live male births. Patients with Haemophilia A have a deficiency or absence of blood coagulation factor VIII (FVIII), an essential component of the intrinsic pathway in the coagulation cascade (*Mannucci et al. 2001*; *Franchini et al. 2013*).

Patients with Haemophilia A, particularly those with severe disease, suffer from bleeding episodes, especially into the joints or muscles, these bleeds often cause pain and can lead to chronic swelling, deformity, reduced mobility and long-term joint damage.

Bleeding is treated with replacement of the missing coagulation factor (FVIII). Prophylactic FVIII replacement therapy has been shown to minimize bleeding events and complications and since the 1990s, recombinant FVIII concentrates have been standard-of-care treatment options for patients with Haemophilia A.

The absence or functional deficiency of FVIII leads to a lifelong bleeding tendency. Common clinical signs of Haemophilia A include easy bruising; prolonged bleeding after trauma or surgery; spontaneous bleeding into joints, muscles, or soft tissues; and intracranial haemorrhage (*World Federation of Haemophilia 2013*).

A further complication is reduced bone mineral density, which is seen in both adults and children with Haemophilia A (*Paschou et al. 2014*). Potential underlying causes include reduced weight-bearing activity, vitamin D deficiency, haemarthropathy, and direct links between coagulation factors and function of osteoblasts and osteoclasts responsible for bone architecture (*Kempton et al. 2015*). The significant negative impact of reduced bone mineral density was recently demonstrated in a single-centre study of 316 patients. The incidence of bone fractures of individuals with Haemophilia A was 22.9 fractures per 1000 patient-years, compared with 9.6 for the general population, and was higher for those with severe versus mild or moderate Haemophilia A but with no difference for those with or without inhibitors (*Gay et al. 2015*). These disease-related issues can have a significant impact on the health-related quality of life (HRQoL) of both adult and adolescent patients (*Brown et al. 2009*).

Haemophilia A is associated with prolonged bleeding after trauma; spontaneous bleeding into joints, muscles, or soft tissues (*World Federation of Haemophilia 2013*), which can have a significant impact on patients' mobility and the HRQoL of both adult and adolescent patients (*Brown et al. 2009*).

Compared with control populations, people with Haemophilia have been shown to have moderate impairment of balance and mobility and reduced levels of physical activity (*Fearn et al. 2010*; *O'Donnell et al. 2014*). Improving mobility and safely increasing activity level in this population are important goals that will result in significant health and quality-of-life benefits (*von Mackensen et al. 2010; Czepa et al. 2013*). Ample scientific evidence and guidelines support the health promoting value of physical activity underlining the importance of assessing activity in adolescents and adults with Haemophilia. According to expert recommendations and the World Health Organization (WHO), adults should perform 10000 steps a day and accumulate at least 150 minutes of moderate-intensity physical activity throughout the week (*WHO 2010; Tudor-Locke C et al. 2011*).

Regular exercise is recommended to patients in order to promote strong muscles, develop balance, and improve fitness, which in return can contribute to healthier joints and diminish the occurrence of bleeds. However, physical activity likely to cause trauma, such as high contact and collision sports, should be avoided. (*Srivastava A et al. 2013*).

As expected, the degree of joint damage correlates with the level of activity. However, this parameter accounts for only a small fraction of the variability in the amount of activity performed by different people with Haemophilia (*Baumgardner et al. 2013*), which is not surprising as level of activity reflects both ability and motivation. Motivation (or lack thereof) is particularly important in people with Haemophilia who are at risk of bleeds with physical activity (*Broderick et al. 2012*), even when receiving standard therapies.

The amount and intensity of physical activity in children and adolescents with Haemophilia has previously been quantified using an accelerometer. However, no study has been performed in the adult Haemophilia population where the sequelae of different bleeds and consequent limitations on activity have been evaluated.

4.1 STUDY RATIONALE

There are few data on physical activity in patients with Haemophilia. Previous studies have generally included small samples of patients and none has been conducted in Italy.

The rationale for conducting this non-interventional study (NIS) is to collect information about activity status, bleeds, health-related quality of life (HRQoL) and health status in patients with moderate or severe haemophilia A without inhibitors, who are being treated in accordance with normal clinical practice.

This NIS aims to provide robust documentation about activity levels, bleeds, HRQoL and health status (in adults/adolescents) in patients with Haemophilia A treated according to local routine clinical practice (receiving FVIII replacement therapy or bypassing agents as either episodic or prophylactic treatment).

Furthermore, new upcoming therapies for haemophilia A will likely continue to change clinical practice. Ranging from new extended half-life replacement therapies, to nonfactor products and gene therapy, these innovative approaches have the potential to enhance the standard of care by decreasing infusion frequency, easing route of administration, in some cases also ensuring more efficacy, reducing the risk of bleeds, and in particular the number of target joint bleeds, all characteristics that could have a significant impact on physical activities and quality of life.

Therefore, in this study it has been considered of interest to collect information on physical activity status bleeds, HRQoL and health status in patients that will start treatment with any new drug, if approved during the course of the study for the treatment of Haemophilia A without factor VIII inhibitors, *i.e.* the population object of the study.

In case of start of treatment with any newly approved treatments during the study, the patient will be observed, on primary and secondary objectives, for a minimum period of 6 months.

The data from this study may be used to compare with data from ongoing interventional studies or to refine assumptions pertaining to patient characteristics, to enhance the design of new interventional or non-interventional studies.

5. RESEARCH QUESTION AND OBJECTIVES

5.1 RESEARCH QUESTION

This NIS is designed to collect information on physical activity status, bleeds, HRQoL, health status in patients with severe or moderate Haemophilia A without inhibitors receiving standard of care treatment, during a period of 12-18 months of routine clinical management.

5.2 OBJECTIVES

5.2.1 Objectives

The primary objective for this study is to document physical activity, particularly in terms of active minutes, steps count and Metabolic Equivalent of Tasks (MET) over the 12 months period, by age categories (12-17, 18-30 and 31-50 years) in patients with haemophilia A without inhibitors .

The secondary objectives for this study are as follows:

- To document physical activity, particularly in terms of active minutes, by ages categories (12-17, 18-30 and 31-50 years), by type of physical activity and by intensity (as per fitness tracker default categorization);

- To describe the observed population in terms of:

  - Number of patients, adherent to WHO Guidelines (*i.e.*, Global Recommendations on Physical Activity for Health) for the definition of physical activity (*WHO 2010*);

  - Number and type of bleeds occurring during routine clinical practice and reported at any occurrence via the Electronic Patient-reported Outcome (ePRO) application;

  - Treatment regimen for Haemophilia A (prophylaxis, preventative treatment before physical activity, treatment for any episode of bleeds), in terms of type of regimen (ondemand vs. prophylaxis), product used and dose;

  - Health-related quality of life (HRQoL) and health status (evaluated at baseline, every three months, and at the end of the study) reported during routine clinical practice, measured using the European Quality of Life-5 Dimensions (EQ-5D-5L) score (adults/adolescents);

  - Dose and frequency of concomitant medications taken to control pain (e.g. nonsteroidal anti-inflammatory drugs [NSAIDs], painkillers);

  - Joint health status of enrolled patients, based on Haemophilia Joint Health Score (HJHS) questionnaire (evaluated at baseline, at six months, and at the end of the study);

- Body mass index (BMI) evaluated at baseline and every three months;
- Number of days away from school (patient) and/or work (patient and caregiver), and age of possible early retirement (caregiver) during the observation period, evaluated through administration of questions (evaluated at baseline, every month, and at the end of the study);
- Number of hospitalization days (patient) during the observation period evaluated through administration of questions (evaluated at baseline, every month, at the end of the study);
- Pain intensity measured using a Visual Analogue Scale (VAS) (evaluated at baseline, every month, and at the end of the study);

• To evaluate adherence to the treatment regimen:

- Documented during planned visits according to source data (ePRO data) in electronic Case Report Forms (eCRF) by the Investigator;

• To describe the active vs. sedentary Haemophiliac patients in terms of:

- Severity of disease;
- Annualized bleeding rate (ABR);
- Pain and use of painkillers;
- Drug regimen adopted;
- HRQoL;
- Hospitalization/missed days at school; - Joint Health Status.

• To describe severe vs. moderate Haemophiliac patients for the above mentioned items.

5.2.2 Exploratory Objectives

The exploratory objectives for this study are as follows:

• To evaluate the relationship between physical activity (type and intensity) and bleedings;

• To evaluate the sleep duration and sleep stage in participant patients;

• To observe patients, on primary and secondary objectives, for additional 6 months if new therapies become commercially available for patients with Haemophilia A without inhibitors against FVIII, during the course of the study and if patients will start such treatments during, the observation period

In the context of this study, newly approved drugs are considered all those newly approved during the course of the study and commercially available for prophylaxis treatment in patients with haemophilia A without inhibitors (See section 4.1).

6. RESEARCH METHODS

6.1 STUDY DESIGN

6.1.1 Overview of Study Design

This is a multicenter, non-interventional, prospective study. The study will be conducted according to the following scheme:

	Observational period	
Baseline	**Standard observational period for all observed patients**	Month 0 to Month 12
	Prolonged observational period if patients start newly approved drugs between Month 6 and Month 12	6 Months after the start of new therapy (*e.g.*, max observation period of 18 months if patients start the newly approved drugs during the last month of standard observational period)

Please refer to Appendix 2 for Data Collection Overview (as per Standard of Care) and to Section 6.4.1 for the description of procedures of data collected during the observational period.

The entire observational period will last 12 months. Patients that will start treatment with any newly approved drugs between Month 6 and Month 12 will complete a 6-month observational period after the switch, and therefore the entire observational period in these patients may be prolonged up to a maximum of 18 months. In the context of this study, newly approved drugs are considered all those newly approved during the course of the study and commercially available for prophylaxis treatment in patients with Haemophilia A without inhibitors

Visits at the clinic will be performed approximately every three months, but some degree of flexibility (*e.g.*, ± 1 month or higher) will be considered according to Investigator's judgment and local clinical practice.

This study will include patients aged ≥ 12 years and ≤ 50 years with severe (FVIII < 1%) or moderate (FVIII ≥ 1 and ≤ 2%, i.e. in the higher range of severity) Haemophilia A without inhibitors against FVIII.

During the study, HRQoL, health status, joint health status will be reported on a pre-determined frequency for 12 months. Physical activity data will be collected daily using a fitness tracker.

Approximately 150 patients overall, 125 patients with severe Haemophilia A and 25 patients with moderate Haemophilia A without inhibitors against FVIII are planned to be enrolled.

Additionally, patients (or patient's legally authorized representative) will be reminded on a monthly basis to report via their ePRO application whether a bleed has occurred and whether treatment for a bleed or treatment to prevent a further bleed has been given. When a bleed occurs, the patient (or patient's legally authorized representative) will be required to report bleed information, including site of bleed, type of bleed, time of each individual bleed (date, time of start and time of end), symptoms of bleed, and treatment for bleed.

Health status will be captured in ePRO via the visual analogue scale (VAS) component of the EQ-5D-5L at baseline, every 3 months and at the end of study.

Physical activity will be measured daily by wearing a fitness tracker continuously during study participation. Patients will be daily reminded to wear the device. A valid day of monitoring is defined as at least 10 wear hours per day. Wear time will be derived though data collected by the fitness tracker.

The reason for the use of coagulation products (*e.g.*, bleeding, prophylaxis, pain, etc.) will be documented by Investigator in source data and reported in the e-CRF. The reason for the use of coagulation products for bleeding treatment, including agent, start time, dose, route of administration, and number of infusions needed to treat the bleed, will be recorded by patients in the ePRO application and will be then transmitted to the eCRF.

Therapy will be recorded by the investigator at baseline visit and it will afterwards be confirmed by the patient in ePRO application. If there are changes to the assigned therapy, the patient will enter therapy variations in ePRO (*e.g.*, dose, frequency, drug name etc.) and data will be then transmitted to the eCRF.

Demographics and results from physical examinations, and vital sign assessments, will only be collected if available from routine clinical practice. No additional diagnostic or monitoring procedures will be applied to the patients outside of routine clinical practice.

Start Date of Study:

The study start date will be the date of the signing of informed consent of the first patient (or caregiver). The planned start date is October 2019.

End of Study:

The end of the study will be the date on which the last patient performs the last visit, this is expected when:

- The last patient completes the 12-month observation period (and patients that start treatment with any newly approved drugs complete a 6-month observational period after the switch), or
- The last patient has died, withdraws consent or is lost to follow up, whichever occurs first, or
- The study has been terminated by the Sponsor, if earlier.

6.1.2 Rationale for Study Design

A non-interventional study design was considered appropriate to evaluate, in adolescent and adult patients with Haemophilia A without inhibitors against FVIII, the amount and intensity of physical activity and the level of limitation of physical activity due to bleeding, in a real-life setting over a 12 months' standard observational period. A prolonged observational period up to a maximum of 18 months is considered, if patients start a newly approved drugs between Month 6 and Month 12. A 6 months' observational period is in fact considered for patients who started

a newly approved drugs during the standard observational period (month 0 to 12) to assess the effects of the change in therapy. Therefore, the scheduled observational period will be 12 months for patients who will start a newly approved drug in the first 6 months of observation and will be prolonged beyond 12 months in patients who will start a newly approved drug between Month 6 and Month 12, up to a 6-month period of observation from the start of the new drug is completed.

As detailed in Section 4, people with haemophilia have impaired balance and mobility and reduced levels of physical activity. Improving mobility and safely and increasing activity levels in this population are important goals that should result in significant health and HRQoL benefits.

Monitoring of the amount and intensity of physical activity in adolescent and adult patients with haemophilia A treated according to local standards of care will provide important information about the appropriateness of treatments for Haemophilia A (as prophylaxis or for the treatment of episodes of bleeding) administered according to routine clinical practice, and on the impact of amount and intensity of physical activity on HRQoL in these patients.

Information on HRQoL will be evaluated using the European Quality of Life-5 Dimensions (EQ5D-5L) questionnaire in both adults and adolescents. HRQoL is an important outcome in the care of patients with Haemophilia (*Brown et al. 2009*). HRQoL in haemophilic patients is multifaceted and impacted by disease symptoms (*e.g.*, pain, bleeding), treatment (prophylactic, on demand, side effects), limitations on daily functioning, anxiety/depression, and time spent in hospital. The goal of measuring HRQoL is to quantify the benefit of treatment from the patient perspective.

Furthermore, this study will also evaluate joint health status in the main joints by means of the Haemophilia Joint Health Score (HJHS) questionnaire.

New upcoming therapies for haemophilia A will likely continue to change clinical practice. Ranging from new extended half-life to nonfactor products and gene therapy, these innovative approaches have the potential to enhance the standard of care by decreasing infusion frequency to increase compliance, promoting prophylaxis, easing route of administration, ensuring in some cases also more efficacy reducing the risk of bleeds, and in particular also the number of target joint bleeds, all characteristics that could have a significant impact on physical activities and quality of life. Therefore, for patients that will start treatment with any newly approved therapy, during the observational period (in case the drugs will be approved for the treatment of Haemophilia A without inhibitors against FVIII during the observational period) the study will also document the effect of the start of the new therapies compared with the previous standard of care.

In the context of this study, newly approved drugs are considered all those newly approved during the course of the study and commercially available for prophylaxis treatment in patients with Haemophilia A without inhibitors.

Rationale for Electronic Patient Reported Outcomes with bring-your-own-device (BYOD)

Advances in technology have significantly increased electronic PRO (ePRO) data collection capabilities and options in clinical trials, observational studies, and registries (*Jones et al. 2013; Wysham, Wolf, Samsa, Abernethy, & LeBlanc, 2017*). ePROs provide more accurate and complete data, improve protocol compliance, prevent secondary data entry errors, pose less administrative burden and have high respondent acceptance (*Coons et al. 2015*).

In order to make study participation more engaging and convenient, an approach that leverages patients' own devices to enable the collection of self-report data ("Bring Your Own Device" [BYOD]) has been previously used. There is strong evidence supporting equivalence between BYOD, paper and a provisioned electronic device to administer PROs composed of typical response scale types (visual analogue, verbal response, and numeric response scales). This equivalence is maintained when migrating between these different formats (*Byrom, Doll, et al., 2018; Byrom, Gwaltney, Slagle, Gnanasakthy, & Muehlhausen, 2018).*

6.1.3 Number of Patients Observed in the Study

The aim is to include a total of 150 patients in the study. Up to 125 patients with severe haemophilia A and 25 patients with moderate haemophilia A without inhibitors against FVIII are planned to be enrolled.

6.1.4 Sites

This study will be conducted at approximately 20 investigational study sites in Italy.

Study sites may be added or substituted if recruitment rates are lower than anticipated

6.2 POPULATION

The study population will include patients aged ≥12 years and ≤50 years with severe or moderate Haemophilia A without inhibitors against FVIII receiving standard of care treatment.

Patients must meet the following criteria for study entry:

1. Signed informed consent
    - Consent/assent will be taken as appropriate, according to age and applicable regulations.
2. Must have an own device compatible with the ePRO application and with the fitness tracker that will be provided to the patient (Fitbit Versa model), please refer to appendix 6 for an exhaustive list of acceptable devices.
3. Must have on his/her own device a data traffic of at least 2 GB in total per month intended only for use of study applications and data transfer. If the data traffic plan is exhausted the patient must be able to connect to a wi-fi network at least once every day in order to transfer the data collected for the study purpose
4. Must accept to run on his/her own device the ePRO application and the fitness tracker application

5. Must be available to turned on daily the bluetooth connection of his/her own device in order to allow the synchronization with the fitness tracker.

6. Ability and willingness to comply with all aspects of the protocol, including completion of questions on the electronic patient reported outcome (ePRO) application (for underage population, ePRO questions can be answered by legally authorized representative if deemed necessary).

7. Ability and willingness to wear the activity device as indicated.

8. Patients aged ≥ 12 years and ≤ 50 years at time of informed consent.

9. Diagnosis of severe (FVIII < 1%) or moderate (FVIII ≥ 1 and ≤ 2%) congenital Haemophilia A.

10. No prior history of a positive inhibitor against FVIII. If patient has a previous history of inhibitor development, the patient must have successfully eradicated inhibitors since 3 years.

11. At least 150 exposure days of FVIII prior to enrolment.

Patients who meet any of the following criteria will be excluded from study entry:

1. Bleeding disorder other than congenital haemophilia A.

2. Ongoing (or planned during the study) immune tolerance induction or FVIII prophylaxis if the patient has currently low title of inhibitors or had inhibitors in the past three years

3. Previous or concomitant autoimmune or connective tissue disease.

4. History of or suspected allergy or intolerance to any of the component of the fitness device (*e.g.*, aluminium anodised).

5. History of clinically significant hypersensitivity associated with monoclonal antibody

6. Obesity (BMI ≥ 30 kg/m^2).

7. Clinically important cardiovascular, metabolic, endocrine disorders or any other concomitant diseases or conditions that could limit the mobility of patients or could represent any risk according to the Investigator's judgment, or that could interfere with the study evaluation parameters.

8. Participation in any other interventional clinical trial, including Roche sponsored, or in any other support program that may include drug administration other than standard clinical practice (*e.g.*, compassionate use, use not in agreement with the authorized indications, patient support programs).

6.2.1 Rationale for Patient Population

The study population will include patients aged ≥12 years and ≤ 50 years with severe or moderate haemophilia A without inhibitors against FVIII.

Patients with haemophilia A without inhibitors against FVIII have a lower risk of bleeding than patient with inhibitors against FVIII (*Kruse-Jarres et al. 2018*). The reduction in risk of bleeding that can be conferred by prophylactic treatment may be such that the benefits of physical activity outweigh this risk. However, there is scarce information on the degree to which risk of bleedings is elevated by physical activity (*Broderick et al. 2012*). The inclusion of patients with Haemophilia A without inhibitors against FVIII, who can practice moderate/intense physical activity, has been considered as an appropriate patient population for the evaluation of this risk.

For a reliable assessment of the level of limitation of physical activity due to bleeding, frequency and intensity of bleeding, and patient's quality of life in patients with Haemophilia A treated according to routine standard of care, it has been considered as appropriate to include patients with Haemophilia A of severe or moderate degree (with the latter category in the higher range of severity, *i.e.*, FVIII ≥ 1 and ≤ 2%), in order to better explore the conditions that may be associated with improvements in physical activity and the categories of patients that can benefit from treatment in common clinical practice.

6.3 VARIABLES

Only data obtained according to routine clinical practice and collected according to the study objectives will be documented in this study.

6.3.1 Primary Variable

The primary variable is:

- Physical activity data collected through a wearable device (*i.e.*, fitness tracker) in terms of active minutes, METs and step counts.

6.3.2 Secondary Variables

The secondary variables are:

- Adherence to WHO Guidelines for the definition of physical activity;
- Date and time of bleed start and end and number of bleeds over time;
- Sites of bleed;
- Types of bleed (spontaneous, traumatic);
- Treatment for bleed (episodic or prophylaxis agent and/ or other agent used, dose, route, start date and time of treatment used);

- Treatment regimen for Haemophilia A (episodic, prophylaxis, preventative treatment before physical activity), in terms of type of regimen (on-demand vs. prophylaxis), product used and dose, and adherence to treatment regimen;
- HRQoL through EQ-5D-5L and health status;
- Dose and frequency of concomitant medications taken to control pain (e.g. NSAIDs, painkillers);
- Joint health status based on HJHS questionnaire;
- BMI;
- Number of days away from school (patient) and/or work (patient and caregiver), and age of possible early retirement (caregiver) during the observation period;
- Number of hospitalization days (patients) during the observation period;
- Pain intensity measured using a VAS;
- Engagement in physical activity (i.e. Active/Sedentary);
- Severity of disease.

6.3.3 Other Variables of Interest

- Newly approved drugs (see section 2 exploratory objectives), if patients will start such therapies during the observation period;
- Sleep duration and stages collected through a wearable device (i.e., fitness tracker).
-

6.4 DATA SOURCES

All data will be recorded on electronic case report forms (eCRFs). The degree of detail and completeness of data collected will be dependent on local clinical practice. Data from source documents should be entered on the eCRF as soon as they become available. Daily physical activity data will be collected continuously via the wearable device (*i.e.*, fitness tracker). HRQoL, VAS for pain, missed days at school (patient) and/or work (patient andcaregiver), age of possible early retirement (caregiver), number of hospitalization days (patients), bleeding information and drugs administered to treat Haemophilia (treatment for bleeds, episodic or prophylactic treatments, and preventative treatment before physical activity) will be recorded by the patient through ePRO application according to protocol requirements (refer to Appendix 2, Data Collection).

6.4.1 Data Collected during the Observation Period

Please see Appendix 2 for the data collection overview (as per standard of care).

During the study, clinical and laboratory assessments will be routinely performed in accordance with current guidelines and local standard of care. When performed during the observational period, available results from the range of assessments described below will be documented in the eCRF.

In the routine care setting, patients with haemophilia A without inhibitors against FVIII are seen regularly (approximately every 3 months) by their treating physicians either for treatment or for regular assessment. However, the proposed assessments and suggested timings for assessments (visits at 3-month intervals) in the protocol/observational plan are not mandatory. It is up to the treating physician to perform the assessments as deemed appropriate and to document the assessments as actually performed in the real clinical setting. For this reason, some flexibility in the planned times for the visits is allowed in this study: an approximately ±1-month or higher time window with respect to the scheduled dates of post-baseline visits (*i.e.*, from Month 3 to Month 12 or later for patients that will start treatment with any newly approved drugs between Month 6 and Month 12) is planned. However, the proposed visit plan is only indicative and may be changed according to local clinical practice. As an example, if a visit is delayed by more than one month beyond the planned time, the visit can be skipped (if considered appropriate by the Investigator) and the patient may attend the next scheduled visit according to the protocol.

During the baseline visit, demographic data, medical history, and confirmation of haemophilia A will be collected from the patient's medical records.

Data collection relative to bleeds, bleeds treatment, HRQoL, VAS will be performed directly by the patients through a dedicated ePRO application, that will be downloaded and will run on the patient's own device (BYOD approach). Patients will input data electronically as required by the study (bleeds, bleeds treatment, HRQoL, VAS) while physical activity data will be collected via a wearable device (*i.e.*, fitness tracker).

After the patients have entered data in the ePRO device, Investigators will evaluate the quality of data entries through the eCRF where the data are transmitted from ePRO: they can follow-up compliance with patients, review data collected and check the plausibility and correctness of the data.

In case of premature study discontinuation, an early termination visit (ETV) will be arranged and the same assessments scheduled for the final visit at the end of the 12-month observational period will be performed.

Details of the study procedures are described below and summarized in Appendix 2.

<u>Informed consent and screening log:</u>

Written informed consent for participation in the study must be obtained before performing any study-specific evaluations. Patients and parents/caregivers (for patients aged 12-17 years) will complete, sign and date an Informed Consent Form.

All baseline evaluations must be completed within 4 weeks prior to the start of the 12-month observational period to confirm that patients meet all eligibility criteria before entering the

observational period. The investigator will maintain a screening log to record details of all patients screened and to confirm eligibility or record reasons for screening failure, as applicable.

Demographic data, medical history, past and concomitant treatments, surgeries and procedures:

Demographic data will be recorded at baseline and will include age, sex, race and ethnicity.

Data of physical activity (*e.g.*, type, covered distance, frequency by days/week) will be recorded.

Medical history will be recorded at baseline and will include clinically significant diseases, procedures, use of alcohol and drugs of abuse within the past year, and medication allergies. In particular, sites should record whether the patient has any history of FVIII inhibitor, anaphylaxis or known thrombophilia. The number of bleeds during the 24 weeks prior to baseline should be documented, as well as the number of school/work days missed and number of days hospitalized during the 24 weeks prior to baseline.

At baseline, all medications taken in the 4 weeks prior to baseline for the treatment of Haemophilia A and other concomitant diseases (including prescription, over-the-counter, and herbal/homeopathic remedies and therapies) will be recorded. Any change in concomitant medications (including dose changes) for the treatment of Haemophilia A or for the treatment of bleeds will be recorded by patients using the ePRO for the entire study duration.

Therapy will be assigned by the investigator at baseline visit and it will afterwards be confirmed by the patient in ePRO application. If there are changes to the assigned therapy, the patient will enter therapy variations in ePRO (*e.g.*, dose, frequency, drug name etc). The investigator will document in eCRF any changes to assigned therapy.

In addition the investigator will document in eCRF any relevant surgeries or procedures performed by the patient during the observation period.

Physical examination:

A complete physical examination, if performed during a routine medical visit, will be done at baseline and at least targeted physical examinations will be performed at all follow-up visits. The physical examination should include (but not necessarily be limited to) the evaluation of head, eye, ear, nose, and throat and include cardiovascular, dermatological, musculoskeletal, respiratory, gastrointestinal, and neurological systems, height (at baseline only) and weight (at all follow-up visits). BMI will be calculated.

Any abnormality identified during baseline should be recorded on the General Medical History and Baseline Conditions of the eCRF. Subsequently, a targeted (*i.e.*, musculoskeletal, dermatological) and/or symptom-driven examination should be conducted as noted in the schedule of assessments or as clinically indicated.

Vital signs:

Vital signs, if measured during a routine medical visit, will be collected at baseline and at all follow-up visits. Vital signs will include measurement of heart and respiratory rate, oral temperature, systolic and diastolic blood pressure.

Electronic patient-reported outcomes (ePRO):

Patient reported data will be collected electronically using two a dedicated study application (ePRO application) and a wearable device (*i.e.*, fitness tracker).

Data collection will be performed by the patients or parents/caregivers (for patients aged 12-17 years) through a dedicated ePRO: an application that runs on the patient's own device (BYOD approach) for data collection and management of subjects. The following ePROs data will be recorded: bleeding data, bleeding treatment (drug, route of administration, dose regimen, date of start and date of end), HRQoL, number of days away from school (patient) and/or work (patient and caregiver), age of possible early retirement (caregiver), number of hospitalization days (patient) and VAS for pain.

Therapy will be assigned by the investigator at baseline visit and it will afterwards be confirmed by the patient in ePRO application. If there are changes to the assigned therapy, the patient will enter therapy variations in ePRO (*e.g.*, dose, frequency, drug name etc.). The investigator will document in eCRF any changes to assigned therapy.

In patients that will start treatment with any newly approved drugs, measurements of parameters through ePRO application will also performed at the time of starting any newly approved drugs.

Study personnel should support the patient to download and install the ePRO application on the patient's own device.

Instructions for completing the ePRO data will be provided to patients and parents/caregivers (for patients aged 12-17 years) by an appropriately trained member of the investigator's staff at the baseline visit. Re-training of patients will be performed at the follow-up visits when necessary.

After entry in the ePRO application, data will migrate in the CRF and the Investigators will evaluate the quality of data entries: they can follow-up compliance with patients, review data collected and check the plausibility and correctness of the data.

Physical activity

Physical activity will be measured daily by wearing a fitness tracker (Fitbit Versa model), continuously during study participation and data will be recorded on the related application that runs on the on the patient's own device.

The following data will be collected using the fitness tracker and transferred on eCRF:

- Daily wear time (as valid/not valid), as a derived field;
- Number of steps taken;

- Distance covered;
- Amount of calories burned;
- Body weight;
- Heart rate;
- Sleep duration and stages;
- Active minutes;
- MET, as a derived field;
- Type of physical activity;
- Amount of calories burned during physical activity;
- Duration of physical activity;
- Number of steps taken during physical activity when applicable (*i.e.*, "Walking" "Running").

Bleeds

In case of bleeds, study patient will report bleed information, including site of bleed, type of bleed, time of each individual bleed (date, start time and end time), symptoms of bleed, and treatment for bleed (*i.e.*, treatment start date, start time and end time, reason, route of administration, type, and dose of injection), if any. In addition, patients will be prompted electronically on a monthly basis to report bleed information as above.

Definition of a bleed:

For the purposes of data analyses, a standardized definition of a bleed, adapted from criteria defined by the Subcommittee on Standards and Criteria, FVIII/FIX subcommittee of the International Society of Thrombosis and Haemostasis, will be utilized in this study (*Blanchette et al. 2014*; *Mahlangu et al. 2014*).

An event is considered a treated bleed if coagulation factors are administered to treat signs or symptoms of bleeding (*e.g.*, pain, swelling, etc.).

- Bleeds starting from the first sign of bleed and ending 72 hours after the last treatment for the bleed, within which any symptoms of bleeding at the same location or injections are ≤ 72 hours apart, are considered the same bleed.
- Any injection to treat the bleed, taken > 72 hours after the preceding injection, is considered the first injection to treat a new bleed at the same location.
- Any bleed at a different location is considered a separate bleed regardless of time from last injection.

- Definition of bleed sites:

Sites of bleed will be defined as follows:

- Target joints: defined as major joints (*e.g.*, hip, elbow, wrist, shoulder, knee, and ankle) into which repeated bleeds occur (frequency of ≥ 3 bleeds into the same joint over the last 24 weeks prior to study entry), - Muscle bleeds, - Other bleeds.

- Definition of bleed types:

The assessment of a bleed will be separated into spontaneous bleeds, traumatic bleeds, and bleeds related to procedure/surgery. Both spontaneous bleeds (i.e., the occurrence of haemorrhage where neither the patient nor a caregiver can identify a reason) and traumatic bleeds (*i.e.*, haemorrhage occurring secondary to an event such as trauma, “strenuous” activity, or “overuse”) will be collected.

Types of bleed will be defined as follows:

- Spontaneous bleeds: bleeds should be classified as spontaneous if a patient records a bleed when there is no known contributing factor such as definite trauma, antecedent “strenuous” activity or “overuse” or “procedure/surgery.” The determination of what constitutes “strenuous” or “overuse” will be at the discretion of the patient. For example, light jogging may be considered “non-strenuous” while sprinting may be considered “strenuous,” lifting of weights for a short period of time may be considered “moderate use” while repetitive weightlifting may be considered “overuse.”

- Traumatic bleeds: bleeds should be classified as traumatic if a patient records a bleed when there is a known or believed reason for the bleed. For example, if a patient is to exercise “strenuously” and then has a bleed in the absence of any obvious injury, the bleed would be recorded as a traumatic bleed because, although no injury occurred, there was antecedent “strenuous” activity. Bleeds subsequent to injuries would certainly be classified as traumatic.

- Bleeds related to procedure/surgery: such as hematomas resulting from any surgeries or invasive procedures (*e.g.*, tooth extractions, venepuncture, or subcutaneous drug administrations) or invasive diagnostic procedures (e.g., lumbar puncture, arterial blood gas determination, or any endoscopy with biopsy, etc.) would not be counted as bleeds. Bleeds related to procedure/surgery are not associated with any trauma except procedure/surgery-induced trauma.

Patients and parents/caregivers (for patients aged 12-17 years) will record bleeds in the ePRO application whenever a bleed occurs, and monthly to confirm that all bleeds have been recorded. Patients will be requested to answer the following question: ‘*Have you experienced any bleed in the last month*?’ In case of a positive answer, for each bleeding episode patients and caregivers will provide information on the above topics as well as on the medication used to treat the bleed.
Haemophilia medications that were taken will also be collected through the ePRO application.

Haemophilia Joint Health Score

The HJHS (Appendix 4) is an instrument developed to measure joint health status and to identify early signs of joint disease in children. This tool assesses joints most commonly affected by bleeding (knees, ankles, and elbows) (*Feldman et al. 2008*). Each of the 6 joints is assessed across 8 domains (Swelling, Duration of Swelling, Atrophy, Crepitus, Flexion Loss, Extension Loss, Pain, and Strength), and a Total Score is calculated as the sum of all joint domain scores. The instrument also includes a measure of Global Gait, which encompasses assessments of 4 skills: walking, stairs, running, and hopping on 1 leg.

The HJHS will be completed at baseline, at six months and at the end of the study.

HRQoL

The patient (or the patient's legally authorized representative) will report via the ePRO application, HRQoL using the EQ-5D-5L questionnaire in both adults and adolescents (Appendix 5).

The EQ-5D-5L is a standardized measure of health status developed by the EuroQol Group in order to provide a simple, generic measure of health for clinical and economic appraisal (*Herdman et al. 2011*). The EQ-5D-5L (Appendix 5) includes five levels of severity in each of the five EuroQol-5D dimensions and the EQ VAS. The descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain/discomfort, anxiety/depression), each dimension having 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems). The EQ VAS records the respondent's self-rated health on a vertical, visual analogue scale numbered from 0 to 100 with endpoints labelled '*the best health you can imagine*' and '*the worst health you can imagine*'.

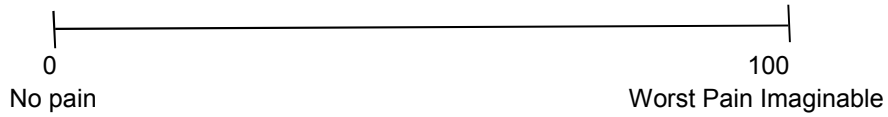
The EQ-5D-5L will be completed at baseline, every three months and at the end of the study, as well as at each episode of bleeding.

VAS for pain (via ePRO)

The intensity of pain in the main joints (elbow, knee, ankle) will be evaluated (at baseline, every month and at the end of the study, as well as at each bleeding episode) by means of a 100 mm VAS and will be recorded through ePRO application.

The VAS is an instrument that measures the amount of pain that a patient feels across a continuum from none to an extreme amount of pain.

Operationally a VAS is usually a horizontal line (see example below), 100 mm in length, anchored by word descriptors at each end, where the left extreme means "No pain = 0" while the right extreme means "Worst Pain Imaginable = 100".



After sitting for 15 minutes, the extent of pain at the injury site will be evaluated in answer to the question: "*How would you describe your injury related pain right now?"*

Patients will mark on the line the point that they feel representing their perceived pain. The VAS score is the distance (in millimeters) from the left end of the line to the point where the patient's mark crossed the line.

It has been demonstrated that the measurement of the response VAS scale collected on paper and by electronic administration, using BYOD or a site-provisioned device, are equivalent. In addition, there is no evidence of a difference in measurement properties of each response scale type across different screen sizes of devices (*Bill Byrom et al. 2018*)

Caregiver burden

The caregiver burden will be evaluated on a monthly basis by collecting the following information: i) the working days lost because of disease; ii) the age of their possible early retirement. Therefore, the productivity loss of caregivers will be estimated considering both the sick leaves of caregiver as well as the economic impact of an early retirement. Data of caregiver burden will be annotated in the ePRO application and then transferred in the eCRF.

In computing the burden for caregivers, the human capital approach will be followed (*Drummond et al. 2005*), valuing the amounts of days and hours of sick leaves by the per hour Italian average wage, according to 2012 Eurostat estimation. Moreover, the charge of early retirement will be estimated by valuing the lost gain from retirement contributions of the working years out of the job market according to Eurostat, and the public expenditure because of the early pension's provision based on Italian Social Insurance Agency (INPS - *Istituto Nazionale della Previdenza Sociale*) data set.

6.4.2 Data Collected at Study Completion

For patients who complete the observation period, the study completion visit will be documented.

Please see Appendix 2 for the data to be collected at the study completion visit.

6.5 SUBJECT, STUDY AND SITE DISCONTINUATION

6.5.1 Subject Withdrawal

Patients have the right at any time and for any reason to withdraw their consent that their data are collected and used for the study. Reasons for withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time;
- Any medical condition that the investigator determines may jeopardize the patient's safety if he/she continues in the study;

- Investigator determines it is in the best interest of the patient;
- Patient's inability or unwillingness to comply with protocol requirements or noncompliance despite appropriate education measures taken by the clinical site.
- Patient died.
- Patient lost to follow-up.

Patients may elect to withdraw from the physical activity monitoring but continue participation in the remainder of the study. If a patient decides to withdraw only from the physical activity monitoring prematurely, the patient will continue with the follow-up visits as per the study protocol. Every effort should be made to obtain information on subjects who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate CRF page. Subjects will not be followed for any reason after consent has been withdrawn. Patients who withdraw from this part of the study will not be replaced.

6.5.2 Study and Site Discontinuation

The study initiator has the right to terminate this study at any time. Reasons for terminating the study may include, but are not limited to, the following:

- Patient enrolment is unsatisfactory.

The Sponsor will notify the physician if the study is placed on hold, or if the Sponsor decides to discontinue the study.

The study initiator has the right to replace a site at any time. Reasons for replacing a site may include, but are not limited to, the following:

- Excessively slow recruitment,
- Poor protocol adherence,
- Inaccurate or incomplete data recording,
- Non-compliance with the Guidelines for Good Pharmacoepidemiological Practices (GPP) or any other pertinent local law or guideline,
- No study activity (*i.e.*, all patients have completed and all obligations have been fulfilled).

6.6 DATA MANAGEMENT

6.6.1 Data Quality Assurance

The contract research organization (CRO) Data Management will identify and implement the most effective data acquisition and management strategy for the clinical trial protocol and deliver datasets which support the protocol objectives. Patient data will be entered into the eCRF and combined with data provided from other sources (*e.g.*, wearable device, ePRO data) in a validated data system.

Clinical data management will be performed in accordance with applicable CRO standards and data cleaning procedures with the objective of removing errors and inconsistencies in the data which would otherwise impact on the analysis and reporting objectives, or the credibility of the Clinical Study Report. Concomitant medications terms will be coded using validated dictionaries.

ePRO data collection will be performed directly by the patients through a dedicated application that runs on the patient's own device (BYOD approach. Physical activity will be measured by wearing a study device (*i.e.*, fitness tracker) in a continuative manner during study participation.

The eCRFs and correction documentation will be maintained in the EDC system audit trail. System backups for data stored at the CRO and records retention for the study data will be consistent with the CRO standard procedures. The CRO will comply with the Sponsor's procedures regarding TMF archiving and record management.

The study data should be verified by the Clinical Research Associate (CRA), *i.e.* the study monitor, with the original data, thereafter all the records and clinical records of the subjects could be accessible. The investigator should allow the access to patient clinical records and the original data should be available for all the study duration. Also the subjects and parents/legal representatives should allow the access to their own clinical records; such condition is cleared and authorized when the subjects supply their authorization for the participation to the clinical study.

6.6.2 Electronic Case Report Forms

Clinical data will be captured using a study specific eCRF using a validated and Code of Federal Regulations (CFR) Part 11 compliant electronic data capture (EDC) system. Sites will receive training and have access to a manual for appropriate eCRF completion.

All eCRFs should be completed by designated trained site staff and reviewed, electronically signed and dated by the Investigator.

At the end of the study, each site will receive their patient's data in an electronic readable format (*i.e.*, PDF format) burned on an adequate media (*e.g.*, CD or DVD). The site will receive a PDF file for each enrolled subject, the file will contain the patient's data and its audit trail.
Data files shall be archived with the site study records.

6.6.3 Source Data Documentation

Clinical monitors will perform ongoing source data verification (SDV) as defined in the Trial Monitoring Plan to confirm that protocol data (*i.e.*, source data) entered in the eCRF by authorized site personnel are accurate, complete, and verifiable from source documents.

Source documents (paper or electronic) are those in which patient data are recorded and documented. They include, but are not limited to, hospital records, clinical and office charts, laboratory notes, memoranda, ePRO data transferred in the database, evaluation checklists, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, patient files, and records kept at laboratories, and medico-technical departments involved in the clinical study.

Before study initiation, the types of source documents that contain study-relevant information will be clearly defined in the Trial Monitoring Plan. The Trial Monitoring Plan defines which kind of source data – if available from clinical routine - can be used for documentation into eCRF. No additional source data creation beyond clinical routine is allowed.

Source documents that are required to verify the validity and completeness of data entered in the eCRF must not be obliterated or destroyed and must be retained per the policy for retention of records described in Section 6.8.4.

To facilitate SDV, the physicians and institutions must provide the Sponsor direct access to applicable source documents and reports for trial-related monitoring, Sponsor audits, and EC review. The participating sites must also allow inspection by applicable health authorities.

6.7 STATISTICAL CONSIDERATIONS

The appointed CRO will be responsible for the statistical analysis of the study. All statistical analyses and data processing will be performed using Statistical Analysis Software (SAS), release 9.4 or later, under Windows 7 or Windows 10 Pro operating system.

The statistical methods planned in this study protocol (see below) will be detailed, agreed and approved in a statistical analysis plan (SAP) which will be finalised before database lock.

Descriptive statistics will be provided in summary tables according to the type of the variable. Continuous variables will be summarized by using number of cases, mean, and standard deviation, median, quartiles and range (*i.e.*, minimum and maximum). Categorical variables will be summarized by using frequency and percent distribution.

Populations for analysis

The following populations will be considered for the analysis:

- Enrolled population: all patients for whom the inclusion/exclusion criteria have been verified and met;

- Evaluable population: all enrolled patients with at least 6 valid months of physical activity evaluations during monitoring through the fitness tracker during the study.

Analysis of demographic an disease characteristics will be performed in the Enrolled population. Analysis of primary, secondary and exploratory variables will be performed in the Evaluable population.

Missing data

Imputation methods for missing values will be discussed and detailed in the SAP as deemed appropriate.

6.7.1 Analyses

Primary variables (*i.e.*, daily evaluations of active minutes, steps count, METs) will be analysed over the 12-18 months' observational period by means of descriptive statistics (e.g. weekly/monthly). The 95% confidence interval (CI) of the mean will be also presented.

Moreover, results will be also shown graphically, if deemed necessary.

Analyses of primary variables will be conducted on patients with established valid measurements from the fitness tracker.

A sensitivity analysis could also be performed evaluating the relationship of primary variables with baseline, demographic or other clinically relevant variables, which will be detailed and described in the SAP.

Secondary variables will be summarized by using descriptive statistics as indicated in general methodology section, according to the type of variable analyzed, at any given time point (where applicable). The 95% CI of the mean change could be also presented.

Particularly, the proportion of patients who will meet WHO recommendations for physical activity will be summarized using descriptive statistics and 95% CIs as well.

The same analysis will be performed on active/sedentary patients and severe/moderate patients.

A further exploratory analysis will be performed in patients that will start treatment with any newly approved drugs during the study. An intra-patient comparison will be performed on pre and post treatment start primary and secondary variables evaluations.

Due to the exploratory nature of this study, no adjustment for multiplicity will be made.

6.7.2 Interim and Final Analyses and Timing of Analyses

One interim analysis is planned, when all enrolled patients have completed 6 months of observation, to have a preliminary evaluation of results and to check if any adjustment in terms of number of required patients or in terms of study procedures may be necessary.

Once the study database is considered clean and before database lock, a data review meeting might be performed. During this meeting the study data will be reviewed to identify potential issues and document decisions taken to address them before the database is locked and the analysis of the data starts. Details of this analysis will be provided in the SAP.

A final analysis will be carried out at the end of study, *i.e.* all patients enrolled and followed up (with no limitations in the period of follow-up) will be included in the data analysis.

6.7.3 Determination of Sample size

Given the exploratory nature and the objectives of this non-interventional study, rather than testing a formal hypothesis, a justification based on epidemiologic data from the Italian registry of congenital bleeding disorders (*Giampaolo et al. 2017*) was considered more appropriate than a power calculation in the traditional fashion or using an estimation approach through the precision of confidence intervals.

Based on data collected from the 54 Hemophilia Treatment Centers, members of the Italian Association of Hemophilia Centres (AICE), it is estimated that the planned number of participants in this study will represent approximately 10-15% of patients with Haemophilia A in Italy in the same age range and category of severity planned for this study. The total sample

size planned is approximately 150 patients overall, 125 patients with severe Haemophilia A and 25 patients with moderate Haemophilia A.

6.8 STUDY DOCUMENTATION, MONITORING, AND ADMINISTRATION

6.8.1 Study Documentation

The physician must maintain adequate and accurate records to enable the conduct of the study to be fully documented, including but not limited to the protocol, protocol amendments, Informed Consent Forms, and documentation of EC and governmental approval/notification. In addition, at the end of the study, the physician will receive the patient data, which include an audit trail containing a complete record of all changes to the data.

6.8.2 Site Audits and Inspections

Site visits could be conducted by the Sponsor or an authorized representative for audit of study data entered in the eCRF and patients' medical records.

The physician will also permit national (Italian or foreign countries) and local health authorities to inspect facilities and records relevant to this study.

In case the site will receive a notice for an inspection from a Regulatory Authority, the Investigator will promptly inform the Sponsor.

6.8.3 Use of Site Computerized Systems

In this study, physical activity will be measured by wearing a study device, in a continuative manner, during study participation. Data collected on physical activity will be transferred to a database. Investigators will access remotely the database, via website, reviewing data input by patients and physical activity adherence and reports.

Data collection will be performed by the patients through a dedicated ePRO: an application that runs on the patient's own device (BYOD approach) for data collection and management of subjects. Patients will input data electronically as required by the study (bleeds, bleeds treatment, HRQoL, VAS).

When clinical observations are entered directly into a computerized medical record system (*i.e.*, in lieu of original hardcopy records), the electronic record can serve as the source document if the system has been validated in accordance with health authority requirements pertaining to computerized systems used in clinical research. An acceptable computerized data collection system allows preservation of the original entry of data. If original data are modified, the system should maintain a viewable audit trail that shows the original data as well as the reason for the change, name of the person making the change, and date of the change.

6.8.4 Retention of Records

Records and documents pertaining to the conduct of this study, including patient's data, Informed Consent Forms and Trial Master File, must be retained by the physician for at least 15 years after completion or discontinuation of the study, or for the length of time required by relevant national (or foreign countries) or local health authorities, whichever is longer. The

Sponsor will inform the Investigator as to when the documents no longer need to be retained. After that period of time, the documents may be destroyed, subject to local regulations.

No records may be disposed of without the written approval of the Sponsor. Written notification should be provided to the Sponsor prior to transferring any records to another party or moving them to another location.

All supporting functional parties will comply with the Sponsor procedures regarding archiving and record management.

6.8.5 Administrative Structure

For this study, a Steering Committee will be organized. The role of the Study Steering Committee is to provide overall supervision of the study and ensure that it is being conducted in accordance with the study protocol, principles of Good Pharmacoepidemiological Practice (GPP), EU Guideline on Good Pharmacovigilance Practices (GVP) and the relevant regulations. The Study Steering Committee should agree the study protocol and any protocol amendments and provide advice to the investigators on all aspects of the study.

6.9 LIMITATIONS OF THE RESEARCH METHOD

Sites participating in this study will not cover the entire Italian territory and, therefore, caution should be used in the generalisation of data collected in this study to the activity status, bleed, HRQoL and health status in patients with Haemophilia A without inhibitors receiving standard of care treatment in routine clinical practice in Italy.

Furthermore, data collected in this study are encompassing an observational period of 12 months (up to 18 months for patients who will start treatment any newly approved drugs) and, therefore, information of data retrieved in this study is to be considered as limited to the study period and cannot be generalised as data of health status in patients with Haemophilia A in the forthcoming years.

7. PROTECTION OF HUMAN SUBJECTS

7.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the Guidelines for GPP published by the International Society of Pharmacoepidemiology (ISPE) and the laws and regulations of the country (Italy) in which the research is conducted.

7.2 INFORMED CONSENT

The Sponsor’s sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a specific patient and parent/caregiver's Informed Consent Form for patients aged 12-17 years) will be provided to each site. The Informed Consent Form will be provided in the local language. The Sponsor must review and approve any proposed deviations from the Sponsor 's sample Informed Consent Forms or any alternate Consent Forms proposed by the site (collectively, the “Consent Forms”) before EC submission. The final Consent Forms approved by the EC must be provided to the Sponsor for health authority submission purposes according to local requirements.

The Consent Forms must be signed and dated by the patient (and by parent/caregiver for patient aged 12-18 years) before performing any study-specific evaluation. The case history or clinical records for each patient shall document the informed consent process and that written informed consent was obtained prior to first documentation of this patient's data in the eCRF.

By signing the form, the patient (and parent/caregiver for patient aged 12-17 years) confirms that he/she has been informed about the study and agrees to pseudonymous data collection, pooling of data with similar scientific data (if applicable), and the possibility of monitoring activities. It is the responsibility of the physician to obtain written informed consent from each patient (and from parent/caregiver for patient aged 12-17 years) participating in the study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The physician must also explain that the patient (and parent/caregiver for patient aged 12-17 years) is completely free to refuse to enter the study or to withdraw from it at any time, for any reason and without losing the benefit of any medical care to which the patient is entitled or is presently receiving.

A copy of each signed Consent Form must be provided to the patient (and to parent/caregiver for patient aged 12-17 years). All signed and dated Consent Forms must remain in each patient's study file or in the site file and must be available for verification by Site Operations Representative at any time.

7.3 ETHICS COMMITTEE

This protocol, the Informed Consent Forms, any information to be given to the patient, and relevant supporting information must be submitted to the EC and reviewed and approved by the EC before the study is initiated. In addition, any patient recruitment materials must be approved by the EC.

7.4 CONFIDENTIALITY

The Sponsor maintains confidentiality standards by coding each patient enrolled in the study through assignment of a unique patient identification number. This means that patient names are not included in datasets that are transmitted to any Sponsor location.

Patient medical information obtained by this study is confidential and may be disclosed to third parties only as permitted by the Informed Consent Form (or separate authorization for use and disclosure of personal health information) signed by the patient, unless permitted or required by law.

Medical information may be given to a patient's personal physician or other appropriate medical personnel responsible for the patient's welfare, for treatment purposes.

Data generated by this study must be available for inspection upon request by representatives of national (or foreign countries) and local health authorities, Sponsor monitors, representatives, and collaborators, and the EC for each study site, as appropriate.

8. MANAGEMENT OF ADVERSE EVENTS

Although adverse event information is not being actively solicited via this protocol, physician/consumers are reminded to report any adverse reactions (for which they suspect a causal role of a product) or special situations either to the marketing authorization holder of the suspected product, via the Roche Adverse Event and Special Situation Reporting Form (SRD-0120176) (for Roche products), or to the concerned competent authorities via the national spontaneous reporting system.

8.1 Reporting Requirements for Adverse Events originating from Patient Reported Outcomes

Although physician/study personnel are not expected to review the PRO data for potential adverse events, if physician/study personnel become aware of a potential adverse event during the review of the PRO questionnaire data, he/she will determine whether the criteria for an adverse event have been met and, if so, these must be reported using the Roche Adverse Event and Special Situation Reporting Form (SRD-0120176) (for Roche medicinal products), or to the concerned competent authorities via the national spontaneous reporting system.

9. PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the Sponsor is dedicated to openly providing information on the study to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The Sponsor will comply with all requirements for publication of study results.

The results of this study may be published or presented at scientific meetings. If this is foreseen, the physician must agree to submit all manuscripts or abstracts to the Sponsor prior to submission for publication or presentation. This allows the Sponsor to protect proprietary information and to provide comments based on information from other studies that may not yet be available to the physician.

In accordance with standard editorial and ethical practice, the Sponsor will generally support publication of multicentre studies only in their entirety and not as individual centre data. In this case, a coordinating physician will be designated by mutual agreement.

Authorship will be determined by mutual agreement and in line with International Committee of Medical Journal Editors' authorship requirements. Any formal publication of the study in which contribution of Sponsor personnel exceeded that of conventional monitoring will be considered as a joint publication by the physician and the appropriate Sponsor personnel.

Any inventions and resulting patents, improvements, and/or know-how originating from the use of data from this study will become and remain the exclusive and unburdened property of the Sponsor, except where agreed otherwise.

10. REFERENCES

Baumgardner JL, Elon L, Antun A, et al. Physical activity and functional abilities in adult males with Haemophilia: a cross-sectional survey from a single US Haemophilia treatment centre. Haemophilia 2013;19(4):551-7.

Blanchette VS, Key NS, Ljung LR, et al. Definitions in Haemophilia: communication from the SSC of the ISTH. J Thromb Haemost 2014;12:1935−9.

Byrom B, Doll H, DPhil, et al. Measurement Equivalence of Patient-Reported Outcome Measure Response Scale Types Collected Using Bring Your Own Device Compared to Paper and a Provisioned Device: Results of a Randomized Equivalence Trial. Value in Health 21 2018; 581-589.

Broderick CR, Herbert RD, Latimer J et al. Association between physical activity and risk of bleeding in children with Haemophilia. JAMA 2012;308(14):1452-9.

Brown TM, Lee WC, Joshi AV, et al. Health-related quality of life and productivity impact in Haemophilia patients with inhibitors. Haemophilia 2009;15:911-7.

Byrom, B., Doll, H., Muehlhausen, W., Flood, E., Cassedy, C., McDowell, B., … McCarthy, M. (2018). Measurement Equivalence of Patient-Reported Outcome Measure Response Scale Types Collected Using Bring Your Own Device Compared to Paper and a Provisioned Device: Results of a Randomized Equivalence Trial. Value in Health, 21(5), 581–589.

Byrom, B., Gwaltney, C., Slagle, A., Gnanasakthy, A., & Muehlhausen, W. (2018). Measurement Equivalence of Patient-Reported Outcome Measures Migrated to Electronic Formats. Therapeutic Innovation & Regulatory Science, 216847901879336. https://doi.org/10.1177/2168479018793369

Coons, S. J., Eremenco, S., Lundy, J. J., O'Donohoe, P., O'Gorman, H., & Malizia, W. (2015). Capturing Patient-Reported Outcome (PRO) Data Electronically: The Past, Present, and Promise of ePRO Measurement in Clinical Trials. Patient, 8(4), 301–309. https://doi.org/10.1007/s40271-014-0090-z

Czepa DS, von Mackensen S, Hilberg T. Haemophilia & Exercise Project (HEP): the impact of 1-year sports therapy programme on physical performance in adult Haemophilia patients. Haemophilia 2013;19(2):194-9.

Drummond M, Sculpher MJ, Torrance GW, et al. Methods for economic Evaluation of Health Care Programmes 3th ed. Oxford University Press, Oxford 2005.

Fearn M, Hill K, Williams S, et al. Balance dysfunction in adults with Haemophilia. Haemophilia 2010;16(4):606-14.

Feldman BM, Funk S, Lundin B, Doria AS, Ljung R, Blanchette V. Musculoskeletal measurement tools from the International Prophylaxis Study Group (IPSG) Haemophilia. 2008;14(Suppl 3):162–9.

Franchini M, Mannucci PM. Haemophilia A in the third millennium. Blood Rev 2013;27:179−84.

Gay ND, Lee SC, Liel MS, et al. Increased fracture rates in people with Haemophilia: a 10year single institution retrospective analysis. Br J Haematol 2015;170(4):584-6.

Giampaolo A, Abbonizio F, Arcieri R, Hassan HJ. Italian Registry of Congenital Bleeding Disorders. J Clin Med 201719;6(3).

Herdman M, Gudex C, Lloyd A, et al. Development and preliminary testing of the new fivelevel version of EQ-5D (EQ-5D-5L). Qual Life Res 2011;20:1727-36.

Jones, K. H., Ford, D. V., Jones, P. A., John, A., Middleton, R. M., Lockhart-Jones, H., … Noble, J. G. (2013). The Physical and Psychological Impact of Multiple Sclerosis Using the MSIS-29 via the Web Portal of the UK MS Register. PLoS ONE, 8(1), 1–9.

Kempton CL, Antoniucci DM, Rodriguez-Merchan ECl. Bone health in persons with Haemophilia. Haemophilia 2015;21(5):568-77.

Kruse-Jarres R, Oldenburg J, Santagostino E, et al. Bleeding events and safety outcomes in persons with Haemophilia A (PWHA) without inhibitors: non- interventional study (NIS) from a real- world setting. Haemophilia 2018; 24(S1): 116.

Mahlangu J, Powell JS, Ragni MV, et al. Phase 3 study of recombinant factor VIII Fc fusion protein in severe Haemophilia A. Blood 2014;123:317-25.

Mannucci PM, Tuddenham EG. The Haemophilias–from royal genes to gene therapy. N Engl J Med 2001;344:1773−9.

O'Donnell DE, Gebke KB. Activity restriction in mild COPD: a challenging clinical problem. Int J Chron Obstruc Pulmon Dis 2014;9:577-88.

Paschou SA, Anagnostis P, Karras S, et al. Bone mineral density in men and children with Haemophilia A and B: a systematic review and meta-analysis. Osteoporos Int 2014;25(10):2399-407.

Srivastava A, Brewer A, Mauser-Bunschoten E, et al. Guidelines for the management of Haemophilia. Haemophilia 2013;19(1):e1–e47.

Troiano RP, Berrigan E, Dodd KW, et al. Physical activity in the United States measured by accelerometer. Med Sci Sports Exerc 2008;40(1):181-8.

Tudor-Locke C, Craig CL, Brown WJ, et al. How many steps/day are enough? For adults. Int J Behav Nutr Phys Act 2011;8:79.

von Mackensen S, Czepa D, Herbsleb M, et al. Development and validation of a new questionnaire for the assessment of subjective physical performance in adult patients with Haemophilia-the HEP-Test-Q. Haemophilia 2010;16(1):170-8.

World Federation of Haemophilia 2013: accessed 11 December 2014. Available from: http://www1.wfh.org/GlobalSurvey/Public_AGS/AGS_Patients_Severity_EN.aspx

[WHO] World Health Organization. Global recommendations on physical activity for health 2010. Available from:
http://www.who.int/dietphysicalactivity/factsheet_recommendations/en/

Wysham, N. G., Wolf, S. P., Samsa, G., Abernethy, A. P., & LeBlanc, T. W. (2017). Integration of Electronic Patient-Reported Outcomes Into Routine Cancer Care: An Analysis of Factors Affecting Data Completeness. JCO Clinical Cancer Informatics, (1), 1–10. https://doi.org/10.1200/CCI.16.00043

Appendix 1 List of Stand-Alone Documents Not Included in the Protocol

Not applicable

Appendix 2 Data Collection Overview (as per Standard of Care)

	Baseline	Observational period			Study Completion/ Early Termination Visit[1]	Patients starting any newly approved drugs between month 6 and month 12[2]		
Visit	**1**	**2**	**3**	**4**	**5**			
Time (months)*	**0**	**3**	**6**	**9**	**12**	**Start of therapy**	**3 post-start**	**6 post-start**
Informed consent[3]	x							
Demographic data	x							
History of physical activity	x							
Medical history and history of Haemophilia (including history of anaphylaxis or known thrombophilia)	x							
Number of bleeds, number of school/work days missed and number of days hospitalized during 24 weeks prior baseline	x							
Inclusion/exclusion criteria	x							
Treatment for Haemophilia (including start of treatment with newly approved drugs)	x	x	x	x	X	x	x	x
Prior (in the 24 weeks before baseline) and Concomitant medications, including coagulation products	x	x	x	x	X	x	x	x

	Baseline	Observational period			Study Completion/ Early Termination Visit[1]	Patients starting any newly approved drugs between month 6 and month 12[2]		
Visit	**1**	**2**	**3**	**4**	**5**			
Time (months)*	**0**	**3**	**6**	**9**	**12**	**Start of therapy**	**3 post-start**	**6 post-start**
Physical examination[4]	x	x	x	x	X		x	x
Vital signs (including height (at baseline only), weight and BMI (at baseline and every 3 months)	x	x	x	x	X		x	x
Downloading of ePRO application and training in its use[5]	x							
Dispensing of fitness tracker and downloading of related application								
Physical activity[6]	x	← Daily →				← Daily →		
Bleeding and treatments for bleeding (via ePRO)[7]	x	← When bleeding occurs →				← When bleeding occurs →		
VAS for pain (via ePRO)[8]	x	← Monthly →				← Monthly →		
EQ-5D-5L (via ePRO) [9]	x	x	x	x	x		x	x
Joint health status (HJHS) [12]	x		x		x			x

	Baseline	Observational period			Study Completion/ Early Termination Visit[1]	Patients starting any newly approved drugs between month 6 and month 12[2]		
Visit	**1**	**2**	**3**	**4**	**5**			
Time (months)*	**0**	**3**	**6**	**9**	**12**	**Start of therapy**	**3 post-start**	**6 post-start**
Days away from school (patients) or work (patients and/or caregivers), age of possible early retirement (caregiver), (via ePRO)[10]		← Monthly →				← Monthly →		
Days of hospitalization related to haemophilia (patients) (via ePRO)		← Monthly →				← Monthly →		
Evaluation of start a newly approved drug therapy		x	x	x	x			
Any relevant surgeries or procedures		x	x	x	x	x	x	x

* Visits at the clinic will be performed approximately every three months, but some degree of flexibility (e.g. ± 1 month) will be considered according to Investigator's judgment and local clinical practice.

[1] In case of early study discontinuation (for any reason), procedures will be those scheduled for Visit 5 (study completion visit)

[2] Patients who will start treatment with any newly approved drugs (see section 2 exploratory objectives), between Month 6 and Month 12 will complete a 6-month observational period after the switch, and therefore the entire observational period in these patients may be prolonged up to 18 months. They will also perform the Study Completion/ Early Termination Visit as their last visit.

[3] The Consent Forms must be signed and dated by the patient (if aged ⩾18 years) and by parent/caregiver (for patient aged 12-17 years) before start of documentation of his/her data in the eCRF.

[4] A complete physical examination will be performed at baseline (if planned as per standard routine of care) and at least targeted physical examinations will be performed at all follow-up visits

[5] The ePRO application downloaded on the patient's own device) will be used by patients to record data on bleeds, bleeds treatment, HRQoL, number of days away from school (patients) or work (patients and/or caregivers), age of possible early retirement (caregiver), number of hospitalization days (patients) and VAS for pain. In patients who will start treatment with any other newly approved drugs (see section 2 exploratory objectives), measurements of the parameters listed above through ePRO application will be also performed at the time of start of treatment with any newly approved drugs, and for at least 6 months following the start of treatment.

[6] Physical activities will be measured by wearing a study device continuously during study participation. At baseline, information about physical activity in the previous 24 weeks will be collected if available.

[7] Bleeding and treatments for bleeds will be reported in a continuous manner, during study participation. Patients will be prompted electronically on a monthly basis to report any bleeds. In case of bleeds, patients will report bleed information, including site of bleed, type of bleed, time of each individual bleed (date, start time and end time), symptoms of bleed, treatment for bleed and health status information. The following information on treatments for bleeds will be reported: agent, start time, dose, route of administration, and number of infusions needed to treat the bleed. At baseline, information about any bleedings which occurred in the previous 24 weeks will be collected.

[8] VAS for pain will be evaluated at baseline, monthly and at the end of study.

[9] EQ-5D-5L for pain will be evaluated at baseline, every 3 months and at the end of study

[10] Evaluated at baseline, monthly and at the end of the study

[11] HJHS will be evaluated at baseline, at 6 months and at the end of the study. HJHS will be also performed at the time of start of treatment with any newly approved drugs, and at 6 months following the start of treatment drugs,

Appendix 3 Haemophilia Joint Health Score

Hemophilia Joint Health Score 2.1 – Summary Score Sheet

	Left Elbow		Right Elbow		Left Knee		Right Knee		Left Ankle		Right Ankle	
Swelling		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Duration (swelling)		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Muscle Atrophy		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Crepitus on motion		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Flexion loss		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Extension loss		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Joint pain		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Strength		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE		☐ NE
Joint Total												

Sum of Joint Totals + ☐

Global Gait Score ☐

(☐ NE included in Gait items)

HJHS Total Score = ☐

NE = Non-Evaluable

Swelling
0 = None
1 = Mild
2 = Moderate
3 = Severe

Duration
0 = No swelling
Or < 6 months
1 = ≥ 6 months

Muscle Atrophy
0 = None
1 = Mild
2 = Severe

Joint Pain
0 = No pain through active range of motion
1 = No pain through active range; only pain on gentle overpressure or palpation
2 = Pain through active range

Crepitus on Motion
0 = None
1 = Mild
2 = Severe

Flexion Loss
0 = < 5°
1 = 5° - 10°
2 = 11° - 20°
3 = > 20°

Extension Loss
(from hyperextension)
0 = < 5°
1 = 5° - 10°
2 = 11° - 20°
3 = > 20°

Strength (Using The Daniels & Worthingham's scale)
Within available ROM
0 = Holds test position against gravity within maximum resistance (gr. 5)
1 = Holds test position against gravity within moderate resistance (but breaks with maximal resistance) (gr. 4)
2 = Holds test position with minimal resistance (gr. 3+) or holds test position against gravity (gr. 3)
3 = Able to partially complete ROM against gravity (gr.3-/2+) Or able to move through ROM gravity eliminated (gr. 2) Or through partial ROM gravity eliminated (gr. 2-)
4 = Trace (gr.1) or no muscle contraction (gr. 0)
NE = Non-Evaluable

Global Gate
0 = All skills are within normal limits
1 = One skill is not within normal limits
2 = Two skills are not within normal limits
3 = Three skills are not within normal limits
4 = No skills are within normal limits
NE = Non-Evaluable

NOTE: there is an accompanying instruction manual and worksheets that are required when administering the HJHS

General comments:

Appendix 4 European Quality of Life-5 Dimensions (EQ-5D-5L)

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

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

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

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

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

PAIN / DISCOMFORT

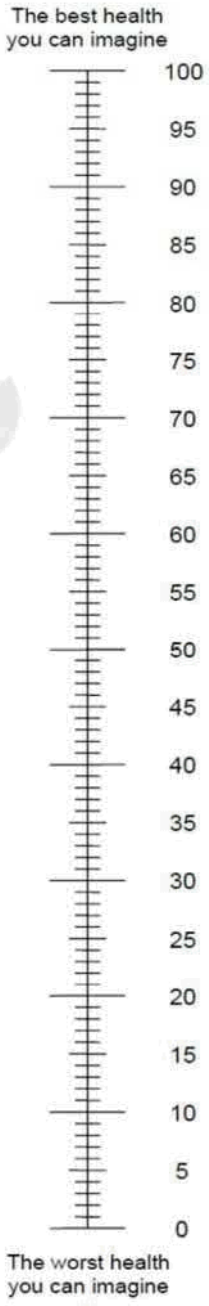
I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

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

YOUR HEALTH TODAY = ☐



Appendix 5 Device compatible with the ePRO application and with the fitness tracker (Fitbit Versa model)

ANDROID DEVICES

Coolpad		
F2		
Google		
Pixel 3	Pixel	Nexus 6
Pixel 3 XL	Pixel XL	Nexus 5x
Pixel 2	Nexus 9	Pixel 2 XL
Nexus 6p		
HTC		
One M9	One M8	One E8
Desire 516*	One Mini 2	Desire 816
Desire 610		
Huawei		
P20 Pro	P20 Lite	P10
Honor 8	Honor 6X	Honor 6
Honor 6 Plus	Mate 9	Ascend P7
Ascend P8		
Lenovo		
Vibe Z2 Pro	Vibe X2	
LG		
V10	G6	G3
G2	G Pro2	
Motorola		
Moto E (2015)	Moto E (2014)	Moto G (2014)
Droid Turbo	Droid Turbo 2	Moto Z
X4	G5S	
OnePlus		
OnePlus One	OnePlus 6	
Samsung		
Galaxy S9	Galaxy S9+	Galaxy S8
Galaxy S8+	Galaxy A8	Galaxy S7
Galaxy S7 Edge	Galaxy S7 Edge Plus	Galaxy S6
Galaxy S6 Edge	Galaxy S6 Active	Galaxy A6
Galaxy S5	Galaxy S5 Active	Galaxy S5 Sport
Galaxy S4	Galaxy S4 mini	Galaxy S4 Active
Galaxy S3 Neo	Galaxy Note 3 Neo	Galaxy Ace Style
Galaxy Note Pro	Galaxy J3	Galaxy Alpha
Galaxy Note 9		
Sony		
Xperia XZ2	Xperia Z3	Compact
Xperia Z3 Dual	Xperia Z2 Ultra	Xperia Z2

Xperia Z1	Xperia Z1 Compact	Xperia ZL
Xperia XA	Xperia T2 Ultra	Xperia M2
Xperia E1		
Xiaomi		
Mi4	Red Mi 2	
ZTE		
Nubia Z7 Max		

** if Android > 4.4

IOS DEVICES

iPhone XS Max	iPhone 6S	iPad Mini 3rd gen
iPhone XS	iPhone 6 Plus	iPad Mini 2nd gen
iPhone XR	iPhone 6	iPad 4th gen
iPhone X	iPhone SE	iPad Air 2
iPhone 8 Plus	iPhone 5S	iPod Touch 6th gen
iPhone 8	iPhone 5c	iPhone 7
iPhone 7 Plus	iPhone 5	iPhone SE
iPhone 6S Plus	iPad Pro 12.9"	iPad Mini 4th gen
iPad Pro 9.7"		