PATIENT REPORTED OUTCOMES BURDENS AND EXPERIENCES STUDY (PROBE): A PRO TOOL DEVELOPMENT INITIATIVE

NCT02439710

28 June 2016

TABLE OF CONTENTS

LIST OF APPENDICES

1. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
BU	Bethesda Units
CDC	Centre for Disease Control (US)
CEO	Chief Executive Officer
CVAD	Central Venous Access Devices
EC	Ethics Committee
FVIII	Factor Eight
HIPAA	Health Insurance Portability and Accountability Act (US)
HRQol	Health Related Quality of Life
ICC	Intraclass Correlation Coefficients
IV	Intravenous
aPCC	activated Prothrombin Complex Concentrates
PRO	Patient Reported Outcomes
PROBE	Patient Reported Outcomes, Burdens, and Experiences
SC	Subcutaneous
SAE	Serious Adverse Event

2. <u>SYNOPSIS</u>

TITLE:	**PATIENT REPORTED OUTCOMES BURDENS AND EXPERIENCES STUDY [PROBE]: A PRO TOOL DEVELOPMENT INITIATIVE**
PROTOCOL NUMBER:	MO39306
VERSION NUMBER:	2,0
DATE OF SYNOPSIS:	28 June 2016
STUDIED MEDICINAL PRODUCT:	None
INDICATION:	Haemophilia
STUDY INITIATOR:	+1 2022 961351
MAIN AUTHOR:	Mark Skinner

Research Question and Objectives Objectives

The primary objective for this study is to validate a PRO instrument for quantifying

burden of disease of haemophilia globally.

Study Design

Test-retest study of PRO instrument. Study
timeline.

First quarter 2016 - Finalize protocol, study questionnaire, website development and related field work materials.

• Second - Fourth quarter 2016 - Country recruitment and begin sampling exercises. Field work anticipated to begin by March 1, 2016 and complete by year-end. Two sampling exercises will be conducted in each country within six months.

• Fourth quarter 2016 - Conduct statistical analysis & project evaluation. Analyze individual country results and assess reproducibility. Evaluate project. Study results will be submitted for publication soon thereafter.

Target Population

Haemophilia patients and a control population, from around 6 difference countries.

Variables

Primary Outcome - Feasibility, measured as:

• Response rate
• Percent complete responses
• Time to completion
• Cost per completed survey

Data Sources

Data will be captured on either web or paper based questionnaire, and transferred t a central database for analysis.

Data Analysis

Descriptive statistics will include the mean of the aggregated scores, the standard deviation and the mean difference between the scores of the first and second questionnaire. Agreement will be assessed using intraclass correlation of Spearman's rank correlation coefficient at the level of individual items and for each composite domain.

Study Size/Determination of Sample Size

In this study approximately 75 subjects will be enrolled across 6 countries.

3. **PROTOCOL AMENDMENTS AND UPDATES**

Any protocol amendments will be prepared by the study initiator.

The Scientific Responsible will seek Counsel / Consultancy for the Protocol and succeeding amendments with his/her competent Ethics Committee.

Protocol amendments/updates so far: none

4.   RATIONALE AND BACKGROUND

Haemophilia A is an X-linked recessive bleeding disorder due to congenital underproduction or dysfunction of the essential coagulation factor VIII (FVIII). The incidence of haemophilia A is approximately 1 in 5,000 live born males, without racial differences, and it accounts for approximately 80% of all cases of haemophilia (Centers for Disease Control and Prevention (CDC) 2014; National Institutes of Health [NIH] 2014; Franchini and Mannucci 2013; World Federation of Hemophilia [WFH] 2013).

Haemophilia A is a lifelong bleeding tendency, and its severity depends on the residual FVIII activity. Approximately 40% of patients have severe (<1% FVIII activity) disease characterized by spontaneous bleedings. Bleeding sites include intra articular, intramuscular, subcutaneous (SC), gastrointestinal, mucocutaneous, and intracranial. Haemophilia A is characterized by recurrent joint bleeds resulting in debilitating joint damage, pain, and limited range of motion. This haemophilic arthropathy has a major impact on health-related quality of life (HRQol) and patients often require surgical intervention, including joint replacement at a young age.

The mainstay of treatment for haemophilia A is replacement of FVIII by recombinant (rFVIII) or plasma derived FVIII concentrates. Intravenous (IV) infusion of these products restores hemostasis, albeit temporarily due to a short half life of 8-12 hrs. Approximately one third of patients develop allo antibodies (inhibitors) against FVIII, and high titer inhibitors (? 5 Bethesda units [BU]/ml) result in neutralization of endogenous or exogenous FVIII. These patients may be treated with bypassing agents (e.g. recombinant FVIIa [rFVIIa] or activated prothrombin complex concentrates [aPCC]).

These products restore hemostasis less reliably, have shorter half-lives, and are associated with severe adverse events (AEs), including thromboembolism. Thus, patients with inhibitors have markedly increased risk of morbidity and mortality (Franchini et al. 2012).

Factor replacement may be given to treat a bleed (i.e., episodic, on demand) or as routine prophylaxis to prevent bleeds by maintaining FVIII level above 1%. With appropriate prophylaxis, nearly half of patients do not bleed spontaneously whereas episodic treatment may be associated with several bleeds each month (Srivastava et al. 2013). Therefore, prophylaxis is superior to episodic treatment (Khawaji et al. 2012) and has been adopted by national and international organizations as the desired treatment approach. However, the burden of treatment (Eton et al. 2013, Mair and May 2014) is extraordinarily onerous, as adequate prophylaxis requires a lifetime of self-administered IV infusion of FVIII 3 4 times each week. In addition, routine IV FVIII therapy relies on venous cannulation skills of patients and their care providers (Hacker et al. 2001). In particular, this issue plagues the care of children and the elderly, often requiring central venous access devices (CVADs [i.e., port a cath]). Although CVADs make prophylaxis feasible, they are associated with complications, including mechanical failure, infection, and thrombosis (Leissinger et al. 201Sa; Leissinger et al. 2015b). Thus, both the

9

disease and its treatment affect patients' HRQoL. In addition to the obvious toll on the quality of patients' lives (Teal et al. 2014), the burden of treatment results in suboptimal care for many who elect to avoid routine prophylaxis or cannot comply with the demanding prophylactic regimen, despite its medical advantage (Geraghty et al. 2006; Lindwall et al. 2006; De Moerloose et al. 2008; Collins et al. 2014; Oldenburg 2015).

Given the unmet need in haemophilia, the disease presents a high burden to patients. It is important that this burden is quantified and appreciated.

4.1 STUDY RATIONALE

Research based on patient-centered datais increasingly valued by government and private payers and utilized in public-policy decisions as part of the cost-benefit justification for high-cost careand treatment. A frequent question of payers is: Will additional investment (to sustain or expand care) improve the livesof persons with hemophilia? There is a significant need to improve our ability to collect, collate, and interpret relevant patient-centered data to support the implementation of comprehensive care, home treatment and preventative treatment regimens (e.g., prophylaxis).

The PROBE study is intended to fill this gap and enhance the direct patient-voice in the delivery of care and move advocacy efforts to sustain and expand carebeyond emotion to arguments grounded in evidence and data.

The overall inventory and the specific metrics developed through PROBE would complement the existing global comparative metrics of the World Federation of Hemophilia (WFH) as provided in the WHF Global Survey (e.g., the percent of patients identifiedvs. expected within a country, amount of treatment products availablewithin a country on a per

capita basis, and the ratioof children to adults survivinginto adulthood). While the WFH global metrics are valued and useful, theydo not **provide** a complete or direct insight as to how patients are fairing within theirhealth caresystem. Theexisting WFH metrics only serve as proxy measures of the impact of careon patient outcomes within a country.

PROBE has an integrated knowledge translation component. Thiscomponent will be manifested through the development and validation of an inventory ableto recode experiential datacontributed by patient organizations to a

valid foundation for evidence-based decision making (e.g.within Health Technology Assessments[HTAs]). PROBE will alsobe useful in raising awareness within the community and the public of the impact of treatment for persons living with hemophilia (PWH) and the value of effective prevention.

5.   **RESEARCH QUESTION AND OBJECTIVES**

5.1   RESEARCH QUESTION

The Patient Reported Outcomes, Burdens, and Experiences (PROBE} Study aims to develop a new global tool to enhance the direct patient-voice in health care decision- making. Government and private payers increasingly value data based on patient- centered outcomes research as part of the overall cost-benefit evaluation of high-cost care and treatment of diseases such as haemophilia.

This emerging dimension of the healthcare environment presents a significant opportunity and urgent need to improve patient organizations' ability to collect and interpret relevant outcomes data. More robust patient reported data will improve advocacy efforts to build comprehensive care programs, promote home treatment and implement preventative treatment regimens thus allowing advocacy arguments to move beyond emotion and anecdote to those grounded in real-world patient experiences and evidence.

With the support of the National Hemophilia Foundation, a global team of investigators will lead a patient focused research project to investigate and directly probe patient perspectives on outcomes they deem relevant to their care.

Through PROBE we will develop and seek to validate the reliability, reproducibility and responsiveness of a low cost, easily administrable inventory for collecting patient self-reported outcomes, burdens and experiences in living with hemophilia. We anticipate that the metrics established through PROBE will allow for comparison of patient outcomes within a country over time and cross-sectionally between countries (regionally and globally}.

5.2   OBJECTIVES

The focus of PROBE will be to investigate and directly probe patients perspectives on outcomes they deem relevant to their care. Through PROBE, we will develop to validate the reliability, reproducibility and responsiveness of a low-cost, easily administrable inventory for collecting patients self-reported outcomes, burdens and experiences in living with hemophilia.

PROBE will be conducted as a multipart study with three Phases. The primary objectives of each phase are distinct but interrelated in their design and funding. They build upon each other in an iterative manner.

This phase, Phase 2, is a pilot feasibility to validate the proof of concept, assess reproducibility and practicality of developing an inventory for large-scale assessment of patient-centred outcomes in people with haemophilia. We expect to be able to compare the effect of different treatment deliver modalities and regimens on patient outcomes.

We anticipate that the metrics established through Phase 2 will allow for comparison of patient outcomes within a countries over time and cross-sectionally between countries (regionally and globally}, thus providing an important new tool to sustain and promote additional health care investment.

11

6. RESEARCH METHODS

6.1 STUDY DESIGN

6.1.1 Overview of Study Design

This study will seek to validate a previously developed PRO instrument, using the principles below.

Step I. Developing a draft inventory. Building upon the work of Phase 1, an inventory consisting of a composite self-administrable questionnaire will be developed during an in-person meeting of the Investigators. The inventory will bundle the EQ-5D-5L instrument along with supplemental questions covering additional domains assessing the impacts of hemophilia on a PWH's life (e.g., pain, independence, educational attainment, employment, activities of daily living) into an integrated questionnaire. The EQ-5D-5L will not be altered. Demographic and treatment related information will be collected for comparison and analysis (Step IV) but not included in the inventory. Where feasible, we will incorporate generic instruments that are already widely accepted by public policy makers.

Step II. Field testing and finalizing the draft inventory. The prototype will be tested for face validity (i.e., the extent to which the inventory covers the concepts and content purported to be covered will be addressed in-depth within the Phase 1 workshop), clarity, and for the time needed for use via one-to-one interviews and user testing with volunteer patients until stable. We will use standard qualitative technology for scale development. Supplemental validity testing will be undertaken as determined necessary following the workshop debrief and based on PROBE Study 5 additional countries recruited for Phase 2 (e.g., those not participating in the Phase 1 workshop). Whether this will occur in country, via focus group, telephone consultation or third-party has not been pre- determined.

Step III. Country Recruitment. The final group of countries selected for the PROBE Phase 2 pilot feasibility study will draw upon the Summit participants. Additional developing and mid-tier countries will be recruited. The final group of countries for the pilot feasibility assessment will be selected to ensure a diversity of geography (e.g., North America, Asia, Africa, Europe, Latin America), economic and care development levels are represented. In total, up to six countries will be invited to participate in Phase

2. Initial expressions of interest or targets to participate have been identified from a range of countries / regions of the world (e.g. Australia, Canada, Denmark, Kenya, India, Ireland, South Africa, US, Vietnam). Recruitment for Phase 2 will begin following launch of Phase 1 and the Barcelona workshop. Resource limitation in Phase 2 design will not allow every possible country combination to be included in the Pilot phase, but PROBE will endeavor to have a diverse country mix. No compensation is contemplated for individual PWH study participants. Additionally, although not contemplated in the budget proposal, reimbursement for associated stdy costs of participating country patient organizations would be considered if required.

Step IV. Test run. Two moderate to large test runs of the inventory will be conducted in each country three months apart to demonstrate reproducibility (Approximately 600 PWH in total - 50 PWH per sampling exercise x six countries x two test runs per country). Both paper and web versions will be developed with translations as required. PWH will be recruited for participation via patient organization contact database and their social media portals. Reproducibility will be assessed based on an analysis of

amount of variability within and across sampling exercises with each country. Responsiveness will be assessed based on response rate and percent complete responses. Reliability will be demonstrated by a combined assessment of measurements for the primary outcomes of Phase 2 (e.g. response rate, complete responses, agreement between exercises, duration, cost and feasibility of execution.) (See: Primary Outcome Variables / Measurement Of Results section below).

Step V. Analysis. The data will be collected at the individual level, but responses will be de-identified and aggregated to perform comparison of outcomes at the population level rather than to allow comparison of outcomes at the individual patient level. We plan to perform three comparisons: among countries, within country over time, within country against national normative data. We will preliminarily assess if normative data are available for the domains explored via existing instruments. When normative data are not available, we will consider strategies to produce a comparator (e.g. surveying non- effected siblings). We will also explore suitable data from other chronic conditions to support the aim of the study. We will conduct a sensitivity analysis to assess the sufficiency of the inventory to measure changes on the impact of care within populations of PWH or overtime using data collected from disease specific questions in the PROBE questionnaire in combination with the EQ-SD. A centralized data collection point will be established. Initial data compilation and cleaning of the database will be incorporated within the web-platform development and reporting agreement (e.g. McMaster University). An analyst experienced in analysis of EQ-SD data and the related study domains will conduct an initial analysis. The Investigators will then evaluate the data and determine the final comparisons and correlations for analysis. Supplemental analyses, data correlation and reporting will utilize/ be contracted for with a university biostatics or health outcomes department experienced in similar studies (e.g. McMaster University, University of Southern California, North Carolina State University).

The specific FDA guidance on Patient Reported Outcomes (FDA, 2009) will be followed. In general, a test-retest experiment is most informative when the time interval chosen between the test and retest is long enough in stable patients to minimize memory effects. However, the choice of the time interval has to take into account the variability of the disease or experience being evaluated (e.g. the potential for change in the condition

over time). In other words, the test-retest experiment is intended to explore than variability in stable patients, and is biased by actual changes in the condition. The FDA guidance acknowledges that "for remitting and relapsing or episodic diseases, test-retest reliability may be difficult or impossible to establish." Therefore, the test-retest reliability can be tested over a variety of periods to satisfy different study protocols or even in different intervals between visits in the same protocol. Examples in the musculoskeletal field span from intervals between the two tests of minutes to several months (Stratford *et al,* 2007; Whitehouse *et al,* 2003; Yang *et al,* 2007; Theiler *et al,* 2002).

Similarly, the sample size for the test-retest study is usually defined, when the measurement properties of the instrument under study are known, by calculating the number of subjects needed to exclude a pre-specified variability. This is almost invariably the case when the test-retest experiment involves a pre-validated instrument used in a different setting or modified or translated. For new instruments, empirical sample sizes, usually from 25 to 100 subjects, and two or more replicates are used.

Study timeline.

- First quarter 2016 - Finalize protocol, study questionnaire, website development and related field work materials.

- Second - Fourth quarter 2016 - Country recruitment and begin sampling exercises. Field work anticipated to begin by March 1, 2016 and complete by year-end. Two sampling exercises will be conducted in each country within six months.

- Fourth quarter 2016 - Conduct statistical analysis & project evaluation. Analyze individual country results and assess reproducibility. Evaluate project. Study results will be submitted for publication soon thereafter.

6.1.2 Rationale for Study Design

Prior phases of the study included development and testing a paper questionnaire for content, relevance, clarity and completeness, as well as assessing methodology and feasibility. This pilot questionnaire was updated for this phase of the PROBE study and has also been adapted to a web-based format.

6.1.3 Number of Subjects Observed in the Study

The study will aim to recruit at least 75 participants in each of 6 countries.

6.1.4 Sites

This study will be conducted in approximately 6 countries.

Additional countries and centers may be added or substituted if underperforming.

6.2 POPULATION

Patients will haemophilia will be invited to participate in the study. Additionally, participants without bleeding disorders will also be asked to participate as a control group.

Participation will be voluntary and data collected anonymously. Subjects will be recruited by the national (or a sub-national e.g. state or chapter) patient organization in the country. Subjects do not need to be the same people in each sampling exercise, but generally the same make-up of people (e.g. members of the patient society).

6.3 VARIABLES

Reproducibility will be assessed based on an analysis of amount of variability within and across sampling exercises with each country. Responsiveness will be assessed based on response rate and percent complete responses. Reliability will be demonstrated by a combined assessment of measurements for the primary outcomes of Phase **2 (e.g.** response rate, complete responses, agreement between exercises, duration, cost and feasibility of execution.)

6.4 DATA SOURCES

PROBE Tool 1- Phase 2 Final

6.4.1 Data Collected during the Observation Period

Participants will be asked to fill out the questionnaire objectively answering the questions for themselves. If completed on paper, the questionnaires will be collected by the patient organization, if by web, the data will be received directly into the PROBE database.

Paper files will be centrally input to the database. Participants will complete the questionnaire in their local language.

Patients will be asked to complete the PRO tool independently of their physician or usual care practice. Thus, no study-specific visits or evaluations are required by this protocol.

6.4.2 Data Collected at Study Completion

Data will be collected from the PRO tool only.

6.5 SUBJECT, STUDY, AND SITE DISCONTINUATION

6.5.1 Subject Discontinuation

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 discontinuation of treatment with the medicinal product or withdrawal from the study may include, but are not limited to, the following:

- Patient withdrawal of consent at any time
- Patient is lost to follow-up.

6.5.2 Withdrawal from Study

Every *effort* should be made to obtain information on patients who withdraw from the study. The primary reason for withdrawal from the study should be documented on the appropriate form. Patients will not be followed for any reason after consent has been withdrawn.

6.5.3 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 enrollment is unsatisfactory

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 any other pertinent local law or guideline

6.6   DATA MANAGEMENT

The study initiator will be responsible for data management of this study, including quality checking of the data. Sites will be responsible for data entry into the system.

6.7   STATISTICAL CONSIDERATIONS

6.7.1   Primary Objective Analyses

Descriptive statistics will include the mean of the aggregated scores, the standard deviation and the mean difference between the scores of the first and second questionnaire. Agreement will be assessed using intraclass correlation of Spearman's rank correlation coefficient at the level of individual items and for each composite domain.

We will further explore the test-retest reliability of PROBE by calculating Lin's concordance correlation (Lin, 1989) coefficient (pc) for both the complete questionnaire and its items separately. This indicates how well a pair of measurements conforms to, or deviates from, a straight line and determines the degree of agreement, i.e. the extent to which the observations conform to a 45° line in a scatter plot when the answer to the first compilation are plotted against those of the second one.

We will use Bland and Altman plots (Bland & Altman, 1986, 2003, 1995) to compare the two replicates and calculate agreement limits.

Finally, we will perform a randomized block analysis of variance and calculate patient and residual error variance components. These variance components will be used to calculate Shrout and Fleiss (Shrout & Fleiss)Type 2,1 intraclass correlation coefficients (ICC2,1 . patient variance/total variance). We will also calculate the SEM as SEMTRT equal to the squared root of the residual variance (Stratford, 2004). Error estimates for score values will be obtained by multiplying SEMs based on test-retest by 1.65, the Z- value associated with a two-sided 90%confidence interval. Minimal detectable change at a 90% confidence level will be calculated as follows: SEMTRT x 1:65 x square root of 2 (Beaton et al, 2002; Beaton, 2001). The square root of 2 term acknowledges two measurements are being compared and the value 1.65 is the Z-value associated with a two-sided 90% confidence interval. The interpretation of minimal detectable change (MDC90) is that 90% of stable patients will display random fluctuations equal to or less than this value when assessed on multiple occasions.

6.7.2   Timing of Analyses

Analysis will be conducted at the end of the study only. No interim analyses are planned.

6.7.3   Determination of Sample size

We will assess the test-retest properties of PROBE in countries on a different sample of patients and controls (individuals who do not personally have a bleeding disorder) from the same country. The test will be administered on paper or via the PROBE website on two separate occasions within a time period short enough not to expect meaningful

variation in the provision of care (e.g. six months}. To this scope we have planned to perform two PROBE measurements at a distance of about six months in six different countries. To be sure to obtain 50 full sets of replicates of which at least 25 will be patients, we will enroll in the study up to 75 subjects. Additional countries may be enrolled to be sure we have 6 complete country sample pairs.

6.7.4 Study Documentation

The country investigators 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 any necessary authority/committee approval or notification.

6.7.5 Site Audits and Inspections

Not applicable

6.7.6 Administrative Structure

The study investigators, listed in Appendix 1, will approve all aspects of study conduct, including protocol deviations and amendments, analysis planning and dissemination of results.

6.8 LIMITATIONS OF THE RESEARCH METHOD

The study will be a validation of the previously developed PRO tool. This evaluation is designed to demonstrate reproducibility, reliability, and patient response. It is not designed to specifically measure the overall burden of the disease in this phase of the study.

7. PROTECTION OF HUMAN SUBJECTS

7.1 COMPLIANCE WITH LAWS AND REGULATIONS

This study will be conducted in full conformance with the laws and regulations of the country in which the research is conducted.

7.2 INFORMED CONSENT

The study initiator's sample Informed Consent Form (and ancillary sample Informed Consent Forms such as a Child's Assent or Caregiver's Informed Consent Form,

if applicable} will be provided to each site.

The Consent Forms must be signed and dated by the subject or the subject's legally authorized representative before start of documentation of his or her data in the questionaire.

By signing the form, the subject 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 subject participating in the study, after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study. The investigator must also explain that the subject 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 subject is entitled or is presently receiving.

A copy of each signed Consent Form must be provided to the subject or the subject's legally authorized representative. All signed and dated Consent Forms must remain in each subject's study file or in the site file and must be available for verification by study monitors at any time.

For sites in the United States, each Consent Form may also include subject authorization to allow use and disclosure of personal health information in compliance with the U.S. Health Insurance Portability and Accountability Act of 1996 (HIPAA). If the site utilizes a separate Authorization Form for subject authorization for use and disclosure of personal health information under the HIPAA regulations, the review,

approval, and other processes outlined above apply except that IRS review and approval may not be required per study site policies.

7.3   INSTITUTIONAL REVIEW BOARD OR ETHICS COMMITTEE

The principal investigator will ensure that the protocol receives approval from any relevant authority or committee in each of the study countries.

7.4   CONFIDENTIALITY

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

Subject 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 subject, unless permitted or required by law.

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

Data generated by this study must be available for inspection upon request by representatives of national and local health authorities, marketing authorization holder monitors, representatives, and collaborators, and the IRS/EC for each study site, as appropriate.

8. **MANAGEMENT OF ADVERSE EVENTS**

Although it is not anticipated that the PROBE Study Team will receive reports of Adverse Events (AE) / Serious Adverse Events (SAE) within the scope of the Study, if the Investigators are made aware of an AE / SAE involving a product manufactured by a study sponsor through the conduct of the study, the Investigators commit to notify sponsor within one (1) business day of actually becoming aware of any significant product complaint, unexpected adverse event, or governmental investigation or inquiry involving a sponsor's product. Study questionnaire may not be reviewed in "real-time." It is understood the study questionnaires may be collected but not reviewed or entered into the PROBE database until the completion of an individual country sampling exercise.

All study data received by PROBE is de-identified and anonymously reported by individual survey participants. The study questionnaire does not allow for identification of individual respondents. No product names are mentioned in the study nor is product specific data being requested from participants.

Although unlikely, there are open text fields where it is theoretically possible that a participant could enter free text that would mention a treatment product by name and directly associate it with a AE/SAE. E.g.:

- Q.8   In the past 12 months, have you experience any problems related to your health?
- Q 24.   Please give a brief history of your treatment regimens during your lifetime (e.g., no treatment, on demand with cryo, immune tolerance, regular prophylaxis with factor, on demand with factor).

To the extent possible, PROBE will report the following details: Date

- Country
- Gender Hemophilia type
- Hemophilia severity Year of birth
- Particulars of the AE/SAE - e.g., product name referenced, associated AE/SAE reported and the context in which it was reported within the study questionnaire

19

PROBE investigators will cooperate and provide a timely response to any request for additional or clarifying information. Investigators will comply with safety reporting requirements pursuant to applicable local laws and regulations in the country/countries where the study is being performed.

9. ## PUBLICATION OF DATA AND PROTECTION OF TRADE SECRETS

Regardless of the outcome of a study, the study initiator is dedicated to openly providing information on the trial to healthcare professionals and to the public, both at scientific congresses and in peer-reviewed journals. The study initiator 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 investigator must agree to submit all manuscripts or abstracts to the study initiator prior to submission for publication or presentation. This allows the study initiator 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, study initiator will generally support publication of multicenter trials only in their entirety and not as individual center 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 the study initiator personnel exceeded that of conventional monitoring will be considered as a joint publication by the physician and the appropriate study initiator's 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 study initiator, except where agreed otherwise.

We plan to discuss the study results in an end-of-study meeting. A paper will be submitted to Haemophilia summarizing the research findings. Abstracts, posters and requests for oral presentation will be considered for relevant national, regional and international meetings (e.g., EAHAD, EHC, ISPOR, ISTH, NHF, and WFH). Study participants will be anonymously acknowledged for their participation. We will report the research findings to the participating patient organizations and once validated PROBE will establish a mechanism to make the inventory widely available for use within the hemophilia community (as Phase 3 of the project).

10. REFERENCES

Beaton, D. (2001) A taxonomy for responsiveness. Journal of Clinical Epidemiology, 54, 1204-1217.

Beaton, D.E., Boers, M. & Wells, GA (2002) Many faces of the minimal clinically important difference (MCID): a literature review and directions for future research. Current Opinion in Rheumatology, 109-114 Available at: http://journals.lww.com/co-rheumatology/Abstract/2002/03000/Many_faces_of_the_minimal_clinically_important.6.a spx [Accessed November 2, 2015].

Bland, J.M. & Altman, D.G. (1986) Statistical methods for assessing agreement between two methods of clinical measurement. Lancet, 1, 307-10.

Bland, J.M. & Altman, D.G. (1995) Comparing methods of measurement: why plotting difference against standard method is misleading. Lancet, 346, 1085-7.

Bland, J.M. & Altman, D.G. (2003) Applying the right statistics: analyses of measurement studies. Ultrasound in obstetrics & gynecology: the official journal of the International Society of Ultrasound in Obstetrics and Gynecology, 22, 85-93.

Centers for Disease Control and Prevention (CDC). Hemophilia Data &Statistics. Accessed April 22, 2014; http://www.cdc.gov/ncbddd/hemophilia/data.html.

Cohen, J. (2013)Statistical Power Analysis for the Behavioral Sciences Elsevier Science.

Collins PW, Young G, Knabe K, et al. Recombinant long-acting glycoPEGylated factor IX in haemophilia 8: a multinational randomized phase 3 trial. Blood 2014;124:3880-6.

Cronbach, L.J. & Warrington, W.G. (1951) Time-limit tests: Estimating their reliability and degree of speeding. Psychometrika, 16, 167-188.

De Moerloose P, Urbancik W, Van Den Berg HM, Richards M. A survey of adherence to haemophilia therapy in six European countries: results and recommendations.

Haemophilia 2008;14:931-8.

Eton DT, Elraiyah TA, Yost KJ, et al. A systematic review of patient-reported measures of burden of treatment in three chronic diseases. Patient Relat Outcome Meas.

2013;5:4:7-20.

Franchini M, Mannucci PM. Hemophilia A in the third millennium. Blood Rev 2013;179-84.

Geraghty S, Dunkley T, Harrington C, et al. Practice patterns in haemophilia A therapy - global progress towards optimal care. Haemophilia 2006;12:75-81.

21

Hacker MR, Geraghty S, Manco-Johnson M. Barriers to compliance with prohylaxis therapy in haemophilia. Haemophilia 2001;7:392-6.

Khawaji M, Astermark J, Berntorp E. Lifelong prophylaxis in a large cohort of adult patients with severe haemophilia: a beneficial effect on orthopaedic outcome and quality of life. Eur J Haematol 2012;88:329-35.

Leissinger CA, Konkle BA, Antunes SV. Prevention of bleeding in hemophilia patients with high-titer inhibitors. Expert Rev Hematol. 2015;8:375-82.

Leissinger CA, Singleton T, Kruse-Jarres R. How I use bypassing therapy for prophylaxis in patients with hemophilia A and inhibitors. Blood. 2015;126:153-9.

Liang, M.H., Fessel, A.H. & Larson, M.G. (1990) Comparisons of five health status instruments for orthopedic evaluation. Medical care, 28, 632-4 2.

Lin, L.1.-K. (1989) A Concordance Correlation Coefficient to Evaluate Reproducibility. Biometrics, 45, 255.

Lindwall K, Colstrup L, Wolter IM, et al. Compliance with treatment and understanding of own disease in patients with severe and moderate haemophilia. Haemophilia 2006;12:47-51.

von Mackensen, S., Czepa, D., Herbsleb, M. & Hilberg, T. (2009) Development and validation of a new questionnaire for the assessment of subjective physical performance in adult patients with haemophilia -the HEP-Test-a. Haemophilia. 170-178.

Mair FS, May CR. Thinking about the burden of treatment. BMJ. 2014;349:g6680.

National Institutes of Health (NIH): National Heart, Lung, and Blood Institute. What Is Hemophilia? Accessed April 22, 2014; https://www.nhlbi.nih.gov/health/health-topics/topics/hemophilia/.

Nunnally, J. (1978) Assessment of reliability. In Psychometric Theory, Nunnally J &

Bernstein IH (eds) pp 225-55. MacGraw-Hill Series.

Oldenburg J. Optimal treatment strategies for hemophilia: achievements and limitations of current prophylactic regimens. Blood 2015;125:2038-44.

Open Science Collaboration, A. (2015) Estimating the reproducibility of psychological science. Science, 349, aac4716- aac4716.

Shrout, P.E. & Fleiss, J.l. Intraclass correlations: Uses in assessing rater reliability.

Stratford, P. (2004) Getting more from the literature: estimating the standard error of measurement from reliability studies. Physiotherapy Canada.

Stratford, P.W., Kennedy, D.M., Woodhouse, L.J. & Spadoni, G.F. (2007) Measurement properties of the WOMAC LK 3.1 pain scale. Osteoarthritis and Cartilage, 15, 266-272.

Streiner, D.L., Norman, G.R. & Cairney, J. (2014)Health Measurement Scales: A Practical Guide to Their Development and Use Oxford University Press.

Teal S, Brohan E, Hetteman Y, et al. Development and psychometric evaluation of a novel tool for assessing patient perception and preference for haemophilia tretmet (HaemoPREF). Haemophilia 2014;20:666-73.

Theiler, R., Spielberger, J., Bischoff, H.A., Bellamy, N., Huber, J. & Kroesen, S. (2002) Clinical evaluation of the WOMAC 3.0 OA index in numeric rating scale format using a computerized touch screen version. Osteoarthritis and Cartilage, 10, 479-481.

Whitehouse, S.L., Lingard, E.A., Katz, J.N. & Learmonth, I.D. (2003) Development and testing of a reduced WOMAC function scale. The Journal of bone and joint surgery.

British volume, 85, 706-711.

World Federation of Hemophilia report on the annual global survey 2013. Accessed 22 June 2015. http://www1.wfh.org/publications/files/pdf-1591.pdfFDA(2009)Guidance for Industry Use in Medical Product Development to Support Labeling Claims Guidance for Industry. , 1-39.

Yang, K.G.A., Raijmakers, N.J.H., Verbout, A.J., Dhert, W.J.A. & Saris, D.B.F. (2007) Validation of the short-form WOMAC function scale for the evaluation of osteoarthritis of the knee. The Journal of bone and joint surgery. British volume, 89, 50-56.

Appendix 1

Study Investigators

- List of responsible parties

Mark Skinner JD, Principal Investigator, Institute for Policy Advancement Ltd. (US)

Alfonso Iorio MD Ph.D. FRCPC, McMaster University, Department of Clinical Epidemiology and Biostatistics (Canada)

Randall Curtis MBA, Factor VIII Computing (US) Neil Frick
MS, National Hemophilia Foundation (US)

Michael Nichol Ph.D. University of Southern California, School of Policy and Planning Development (US)

Declan Noone, Irish Hemophilia Society (Ireland) Brian
O'Mahony, Irish Hemophilia Society (Ireland) David Page,
Canadian Hemophilia Society (Canada)

Jeff Stonebraker Ph.D., North Carolina State University Poole College of Management (US)