Author’s response to reviews

Title: The Patient Reported Outcomes, Burdens and Experiences (PROBE) Project: Development and Evaluation of a questionnaire assessing patient reported outcomes in people with hemophilia

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Author’s response to reviews:

Re: PAFS-D-17-00110

The Patient Reported Outcomes, Burdens and Experiences (PROBE) Project: Development and Evaluation

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Pilot and Feasibility Studies
Dear Editor and reviewers,

We would like to resubmit for publication the revised version of manuscript #PAFS-D-17-00110 “The Patient Reported Outcomes, Burdens and Experiences (PROBE) Project: Development and Evaluation” We appreciated the tremendously helpful comments of the reviewers. The following is a point-by-point response to each reviewer comment.

Editorial Comments

Please make the aims of this paper much clearer. In the methods, three aims are given (a, b and c). However, very little information/data is given to support these - especially a. I would advise making this paper much more focused and including methodology and data, with less description of meetings which could be summarised more (as per reviewer 1 & 2). There are also many places where shorter sentences and a less verbose writing style would aid the reader e.g. lines 120-121. Please undertake a full proof read of the manuscript. Please also take a moment to check our website at http://pafs.edmgr.com/ for any additional comments that were saved as attachments.

We thank the editor for this comment. The manuscript was revised, many sentences shortened and focused on the objectives of the study. We have significantly reduced the length of some sections, and expanded others as request. The resulting revised manuscript is non-significantly longer.

Reviewer #1: Thank you for this interesting and well written paper. I have a few comments as follows:

1. The title does not give a full picture of the subject of the study. It would capture the attention of readers interested in haemophilia and or PROMs work better if the title read something like "The Patient Reported Outcomes, Burdens and Experiences (PROBE) project: development and evaluation of a questionnaire to assess patient reported outcomes in people with haemophilia".

We thank the reviewer for the suggestion. The title of this manuscript has been modified as suggested.
2. A flow diagram depicting the stages of the project would be really helpful as it is quite a complex process and there are a lot of acronyms involved which can make it hard to follow when reading just text.

A flow diagram was added (Figure 1).

3. Were people with haemophilia (other than those in the investigators group) involved at the HERO summit in developing the outcomes of importance to patients? It is not clear whether these outcomes were put forwards by patients themselves or purely identified by professionals and the literature review process.

Yes, the identification of the core outcomes was conducted by literature review and through the discussion among HERO Summit delegates (people with hemophilia, parents and caregivers, hemophilia specialists and researchers). The text was revised beginning on page 12, line 206.

The new text now reads: “Forty-eight delegates from 18 countries and a range of backgrounds within the hemophilia community (PWH, parents, caregivers, hemophilia specialists and researchers) gathered at the Haemophilia Experiences, Results and Opportunities Summit (HERO Summit).”

4. It would be interesting to know in what ways the focus groups influenced the design of the questionnaire. This seems to be the stage which involved PWH most directly but the ‘results’ of the focus groups and the refinement in response to the focus groups is not described.

We have added text to amplify the discussion of PWH involvement on page 12-13.

You are correct, thanks for the comment. Patients were fundamentally instrumental in helping to shape the questionnaire definitions of acute and chronic pain, identify elements for pick lists – e.g., areas of daily living where they had difficulty, relevant co-morbidities. Based on focus group and field work feedback we added items to the pick list (e.g. oral health related issues and gynecological issues). Likewise, we included questions addressing issues using both patient friendly terminology and clinical definitions to compare and contrast between the two (e.g. target joints). In several instances, as our fieldwork expanded to new countries we revised and expanded pick-list options – e.g., when asking about adaptive technologies they use. The contribution of the focus group was mainly intended to ensure that the questions were asked clearly, and were addressing with appropriate face validity living experiences of the patients, particularly within the domains initially identified as most important. The wordsmithing, editing and clarification process provided by the focus group was instrumental in making the question clear and crisp, as per patient judgment.
5. Lines 182-184 mention full psychometric analysis upon successful completion of 'this proof of concept'. Does this mean after the feasibility testing? It would be helpful to state this if so.

The sentence was revised on page 9, line 150.

It now reads: “A full psychometric analysis including a validation study and test-retest reliability study were scheduled upon the successful completion of this refinement phase.”

6. Line 220 - typo 'recruit' should be 'recruitment'.

The typo was edited.

7. Lines 233-235 - the objectives are stated here. Could this sentence be moved to the start of the 'Feasibility study' section for clarity? i.e. Line 207.

Please see the response to the editor above. We have revised the sequence of the main text and the abstract according to the objectives now stated at the outset of the paper in Lines 99-107.

Overall this is a well designed and ambitious piece of work, collecting data from a large number of countries to secure diverse patient input into the development of this measure.

Thank you, we appreciate the comment.

Reviewer #2: General comments

This paper reports on a multi-country pilot study whose overarching objective is to develop a questionnaire to gather data on outcomes relevant to those with haemophilia.

Congratulations on the completion of such an ambitious and wide-reaching study. I intend this to be constructive criticism and hope you will accept it as such. I enjoyed reading the first half of your paper and the project itself sounds fascinating, however, I do not think that the work presented in this paper is currently strong enough for publication. That said, you clearly have enough data that has gone unreported to remedy this. My main problem with this paper is that I am not sure how interesting or instructive it is to a more general audience. I think firstly, the qualitative work that went into the construction, i.e., the development, refinement and
finalisation of the measure and secondly, some initial psychometric properties of the measure need to be reported here.

The details regarding the construction of the tool, something I would have been very interested to read, are simply presented as methodology and not elaborated upon in the results. I would have liked to have read, e.g., i) more information from the focus groups and interviews on how exactly the tool was refined, ii) more details of how the questionnaire was finalised, and specifically how completeness, relevance, and clarity were defined and assessed, iii) the domain structure of the tool (i.e. the theoretical domains, how many items measuring each theoretical domain, etc.), iv) how the tool is intended to be scored, v) any translation issues that emerged, and, vi) most importantly, specifically, what kinds of things the scores will be used for and how this will be of benefit to stakeholders. N.B. you show that the tool is likely to be low-cost, but you do not spell out the benefits well enough, to my mind.

Thanks for your comments and suggestions. In order:

i) We have provided more information on the focus group and refinement process (page 13, line 225-245)

ii) We have provided more details of how the questionnaire was finalised, and specifically how completeness, relevance, and clarity were defined and assessed in the subsequent section (page 14, line 246-268)

iii) The questionnaire domains are discussed on Page 15

iv) The scoring is discussed on Page 15. “Scaling responses are dichotomous (yes or no) and frequency. Frequency questions are answered on a seven-point Likert scale (never, rarely, occasionally, sometimes, frequently, very frequently and all of the time).”

v) The translation process is discussed beginning on line 250, page 14. Other than the usual lengthy time required to review and obtain local feedback no specific problems with translation were identified.
vi) The potential uses, benefits and how PROBE data will be used is addressed throughout the discussion. A couple of examples:

Beginning on line 84 – “Research including or principally focusing on real-world evidence and patient reported outcomes (PRO) is increasingly valued by relevant stakeholders, including governments, regulators [11,13,14], health care agencies, health technology assessment (HTA) agencies [16], private payers and policy makers [12,15]. Patients have unique perspectives and may consider issues differently than regulators, manufacturers, scientists, clinicians and payers [11]. The ability to collect and interpret relevant PRO to support the implementation of the prophylactic treatment, home care and integrated disease management (“comprehensive care”) is becoming more and more relevant to ensure optimal care to PWH [12, 13].”

Beginning on Line 325 – “The main goal in developing the PROBE questionnaire was to enable the collection of data to be used to improve treatment for hemophilia, including supporting comparative effectiveness analysis. For those health care settings moving toward value-based health care [22, 23], the capacity to measure and compare the impact of disease and treatment interventions on the life experiences of patients is critical. In this perspective, it is essential to measure HRQoL with a non-specific instrument, to allow comparison with medical interventions in other disease fields.”

vii) We added the following paragraph beginning on line 353, page 18

“The interest of health care agencies, private payers and policy makers for patient-reported outcomes (PRO) is continuously increasing. Cost and expertise to develop a robust and reliable data collection and analysis plan is a known challenge for NGOs. There is a substantial need to improve capacity to collect and interpret relevant PRO data to support implementation of patient-centered research and advocacy to obtain optimal care in hemophilia. PROBE has demonstrated that it can reliably address this need and its related challenges through establishment of a low cost, low burden and reliable data collection framework.”

Given the relatively large amount of data you have, I would have liked to have read about the initial psychometric properties of the items, and seen the items themselves. If this is not possible for commercial reasons, then perhaps some summary of the item could be used as proxy rather than the final wording. Specifically, if you are intending to construct a score, I would have liked to have seen, e.g., i) Item statistics (facility values, point biserial), ii) reliability statistics
(Cronbach’s alpha, alpha if removed), and, iii) initial scores across countries. I know that this is a pilot study, but 656+ participants is more than enough for initial, and valuable, psychometric assessment. The abovementioned additional information is all related to the piloting and construction of the first iteration of your tool. My intuition is that you are intending to publish this in additional papers. Clearly, you have too much for one single paper, but it is my opinion that this paper, as it stands, is "too thin" and needs strengthening to be suitable for publication.

We understand the reviewer’s concern. Unfortunately, this manuscript aims to describe the rationale of the PROBE study, the development of the research group and research network and the feasibility of the implementation of the PROBE questionnaire. Subsequently, we have conducted additional research and that has led to a full psychometric assessment of the PROBE questionnaire. Given the unique protocol of building a patient-led research network, completing and publishing these results on the feasibility assessment was deemed by the investigators, participating patient organizations and our supporters as an important step to establish the PROBE project for the future. The psychometric paper is under consideration for publication at the moment. We would be pleased to confidentially provide a copy to the referee through the editorial platform if requested.

Additional issues are:

i) It seems that you seem to mix up the objectives of the project and the objectives of the part of the project reported in the paper, at times. This is very confusing for the reader. I only worked about what the paper was reporting on out half way through reading it. Please tell me what the specific objectives of this paper is in the abstract.

We agreed with the reviewer, we have revised the sequence of the abstract and main text according to the objectives of this current study.

ii) I feel you often present more detail than is needed for the general reader; e.g., giving exact dates of meetings, too much description research group (we all do this but it is a bit tedious for a general reader).

We removed details of the meeting from the methods section as suggested. We provided the essential details in the results section.

iii) Sometimes you stray a bit far from the path of plain English, e.g., "through an iterative, bi-directional, and non-structured consultation approach" (we all do this, but maybe just reign it in).
We acknowledge the limitation. The entire manuscript has been proofread by English mother tongue co-authors. Specifically, the sentence highlighted has been dropped.

Major issues

P8L107-10: I do not really know what this sentence means and by extension what your objective are. Please could you nudge the language towards plain English.

The sentences were revised.

P14L242-243: Is this a good way of calculating cost per questionnaire? Isn't it the case that the more questionnaires are collected the lower the cost per questionnaire, i.e. economies of scale?

We agreed with the reviewer with the number of questionnaires may impact the cost of implementing. On the other hand, we expect many NGO collecting a fixed number of questionnaires per year, and we think it is important for them to have a rough estimate of the base cost for running PROBE. There would be other factors that influence the cost, for example, local wage rate, local cost of transportation or local cost of mail. We added the sentences discussing the limitation of cost evaluation in the discussion, Page 20. Additionally, understanding the resource use (staff/volunteer time) associated with running the project was identified early on by the participating NGOs as a critical factor in determining if they would be able to sustain participation in PROBE over time. Although not reported in the paper, in the post research survey completed by participating NGOs, no NGO reported staff time as a barrier to conducting the survey again, only one of the 18 indicated the volunteer time required could be a barrier to participating again. This is the sentence we added beginning at the bottom of page 19:

“Finally, there are several factors that may impact the cost of questionnaire implementation in multiple countries which we have not been able to account for completely, for example, wage rate, cost of transportation rate, cost of mailing rate or number of questionnaire distributed and collected. The cost per questionnaire provided should be considered as a guide, not a final estimate.”

P13L233-236: Please can you state this objective, in this way, earlier? It is only after reading this line that I have worked out what the point of the study is. Previous formulations of the objectives did not really get this across.
The following text summarizing the general objectives was added early in the paper (Lines 97-104). Thank you for the suggestion. The flow of the paper has been rearranged accordingly.

“The PROBE Project aims to implement a structured data collection of PRO across several countries and covering a wide spectrum of health economic environments, to build a robust evidence base for comparative effectiveness, outcome research, evidence-based decision making, and advocacy. To accomplish these overarching goals, three intermediate objectives have been identified for this phase of research: a) develop a patient-led research network; b) develop a standardized questionnaire to gather PRO; and c) perform a feasibility study. Figure 1 demonstrates the flow diagram of the process of the PROBE Project.”

Minor issues

P4L49: Briefly say what kind of experiential data.

To clarify, we have used a more commonly understood phrasing. We revised sentences in both the abstract line 58 and conclusion line 387 to read –

“PROBE proved the feasibility to engage diverse patient communities in the structured generation of real-world outcomes data at all research stages”.

P4L59: Briefly say what the "EQ-5D-5L" and "EQ-VAS" are here.

We revised the text beginning on line 47 and more details in the main text (line 262).

Country specific language versions of the EuroQol 5-dimension 5-level instrument (EQ-5D-5L) a standardized measure of health status developed by the EuroQol Group which consists of the following dimensions: mobility, self-care, usual activities, pain or discomfort and anxiety or depression, and the EuroQol visual analog scale (EQ-VAS) were incorporated and used with permission of the EuroQol Research Foundation
P4L61: "...recruiting 656 participants. Most participants (474, 71%) completed the questionnaire...". Just say 71% of participants, no need to say exactly how many, or use the qualifier "mostly".

We revised the sentence as suggested.

P6L82: In British English this would be "capable of maintaining". Maybe check "Capable to maintain" is acceptable in American English.

We revised the sentence as suggested.

P6L87: You say "Assessment of patient important outcomes beyond bleeding frequency and functional status, including for example burden of treatment, impact on lifestyle and life choices are major aspects that need to be quantified". Could you just add a few words to the end of this sentence to say why this is true? E.g., "in order to ensure patient centred treatment" It would tee up the following paragraph much better.

We have added the paragraph with reference as suggested. The new text beginning on line 72 now reads:

Assessment of patient important outcomes beyond bleeding frequency and functional status, including for example burden of treatment, impact on lifestyle and life choices are major aspects that need to be quantified. Recently, the National Hemophilia Foundation – McMaster University Guideline on Care Models for Hemophilia Management identified the important outcomes that patients' value [10]. Those outcomes are mortality, missed days of school or work, number of emergency room visits, length of hospital stay, quality of life, joint status, educational attainment, patient adherence and patient knowledge. However, bleeding or bleeding rates were not considered as an important outcome.

P6L92: Move "(HTA)") to directly follow the words for which it stands, i.e., move it to before the word "agencies"

The sentence was edited as suggested.
P6L93 I would say "… patients have unique perspectives and may consider …".

The sentence was revised as suggested.

P10L149 - 150: Why are the date and place important to the reader?

We removed the detail of meetings, including date and place from the main text.

P8L110: "overarching goal". Are there not multiple goals, this is unclear.

We clarified and differentiated between the overarching PROBE objectives and the specific intermediate objectives reported in this paper (Lines 97-104):

The PROBE Project aims to implement a structured data collection of PRO across several countries and covering a wide spectrum of health economic environments, to build a robust evidence base for comparative effectiveness, outcome research, evidence-based decision making, and advocacy. To accomplish these overarching goals, three intermediate objectives have been identified for this phase of research: a) develop a patient-led research network; b) develop a standardized questionnaire to gather PRO; and c) perform a feasibility study. Figure 1 demonstrates the flow diagram of the process of the PROBE Project.

P8L114 - P9L131: I am not sure why this much detail about the research group's formulation is relevant or interesting in this paper.

We have shortened the methods section and removed some information as suggested.

P9L139: Be more specific than "geography".
The sentence was revised. See new text on line 126: “The selection of the countries for the pilot was performed by the investigators based on the following parameters: regions (North America, South America, Europe, Western Pacific, Asia or Africa), diversity in access to treatment product, health care system development level, health benefit coverage model and payer typology, local capacity to implement the requested operations.”

P11L182: What do you mean by "ancillary material"?

This was referring to the ancillary fieldwork materials provided to the NGOs for use in executing the study in their country, the participant survey (Appendix 1), sample recruitment materials for use by the NGOs, and the post study NGO survey to identify costs and barriers (summarized in Table 1). To avoid confusion, given it is not essential to state this in the paper we have deleted the clause here. The core focus of interest here is the clarity and content of the questionnaire itself.

P11L185: What do you mean by "completeness relevance"? Do you mean content validity?

We intend to describe the completeness of the questionnaire for measuring all domains assessing patient reported outcomes. We revised the sentence to make it clearer.

P12L200: I am not sure what you mean by "grade level scoring".

Grade level scoring is used extensively in the field of education to make it easier for teachers, parents, librarians, and others to judge the readability level. We understand it is also commonly used with survey instruments. We undertook the scoring to ensure the language of the questionnaire was at an appropriate level for the expected participants. We have changed accordingly to clarify.

P14245-P15L266: I think that this paragraph belongs in the methodology.

We revised the main text as described above.
Nitpicking

P8L118 Why use capital C on "Co-investigators"?

Edited

P8L116: too many commas after MS

Edited

P9L136-137: "through an iterative, bi-directional, and non-structured consultation approach". Unless this is key terminology that I am entirely ignorant of, I am not sure it adds anything to the substantive meaning of the text. If it does add something be specific about what it adds, in plain English.

We have simplified the text. As an FYI, it was through this process that we identified the key metrics to evaluate the success and sustain NGO participation in future phases of the work. This process helped to produce the post study survey used to calculate cost and time burden (summarized in Table 1).

P9L138: Why capital I on Investigators?

The word was edited throughout the manuscript.

P10L165: Perhaps use a weightier verb than scan.

The sentence was revised.

P9L140: The "and" is in the wrong place.

Edited

Best regards,
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