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New Therapies for haemophilia: can we achieve new goals?

Alfonso Iorio (Canada)

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Disclosures

- Co-I of the PROBE project
- No personal honoraria

- McMaster University has received project based funding via research or service agreements from Bayer, CSL, Grifols, NovoNordisk, Octapharma, Pfizer, Roche, Sobi and Takeda/Shire (formerly Baxter and Baxalta).

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Objective

Measuring

the overall net benefit
of
The treatment/(cure)
for a
rare chronic disease
over
the entire life span

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Collect and report well specified outcomes within clinical trials	Increase predictability and consistency of payer / HTA appraisal when making coverage decisions	Shared decision-making using outcomes meaningful to the quality of life and functioning of patients
Market Authorization	Market Access	On-Market Use

Consistent collection and reporting of relevant and well-specified outcomes

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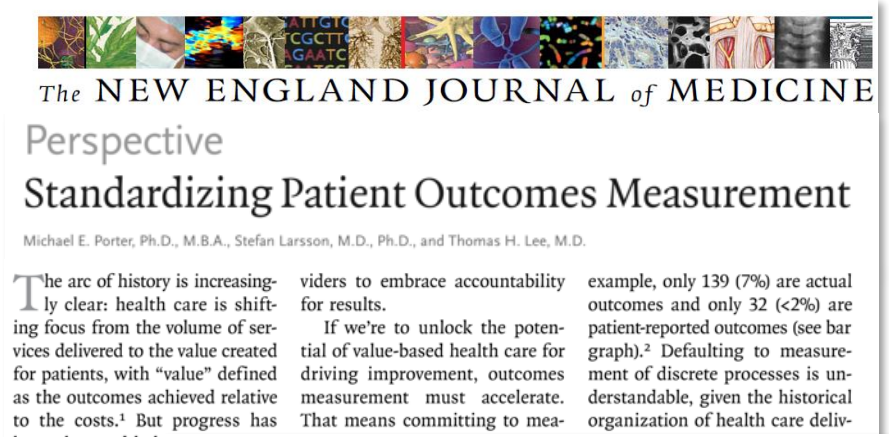
Value in Healthcare = Value Created for Patients

- Historically, outcomes measurement has focused on clinical status and left out functional status
- What matters to patients are outcomes that encompass the whole cycle of care


The NEW ENGLAND JOURNAL of MEDICINE

Perspective

Standardizing Patient Outcomes Measurement

Michael E. Porter, Ph.D., M.B.A., Stefan Larsson, M.D., Ph.D., and Thomas H. Lee, M.D.

The arc of history is increasingly clear: health care is shifting focus from the volume of services delivered to the value created for patients, with "value" defined as the outcomes achieved relative to the costs.[1] But progress has been slow and hal
cause measuremer
that matter to patie
survival, remains l
many conditions,
outcome whose me
to differentiate
merely competent

viders to embrace accountability for results.

If we're to unlock the potential of value-based health care for driving improvement, outcomes measurement must accelerate. That means committing to mea-

example, only 139 (7%) are actual outcomes and only 32 (<2%) are patient-reported outcomes (see bar graph).[2] Defaulting to measurement of discrete processes is understandable, given the historical organization of health care deliv-


Perspective

DECEMBER 23, 2010

What Is Value in Health Care?

Michael E. Porter, Ph.D.

In any field, improving performance and accountability depends on having a shared goal that unites the interests and activities of all stakeholders. In health care, however, stakeholders have

myriad, often conflicting goals,

Value — neither an abstract

value is a central challenge. Nor is value measured by the process of care used; process measurement and improvement are important tactics but are no substitutes for measuring outcomes and costs.

Dolan G, Nugent D, Goodman C, O'Mahony B. A Patient-centered Value Framework For Healthcare In Hemophilia. Int J Technol Assess Health Care. 2017 Jan 12;33(S1):8–9.

Konkle BA, Skinner M, Iorio A. Hemophilia trials in the twenty-first century: Defining patient important outcomes. Res Pract Thromb Haemost. 2019 Mar 12;(January):1–9.

Porter ME, et al. N Engl J Med 2010, 2016

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Value – A Matter of Perspective

Patients have a unique perspective and will consider issues differently than regulators, manufacturers, scientists, clinicians and payers.[1]

[1]FDA Patient Focused Drug Development Initiative

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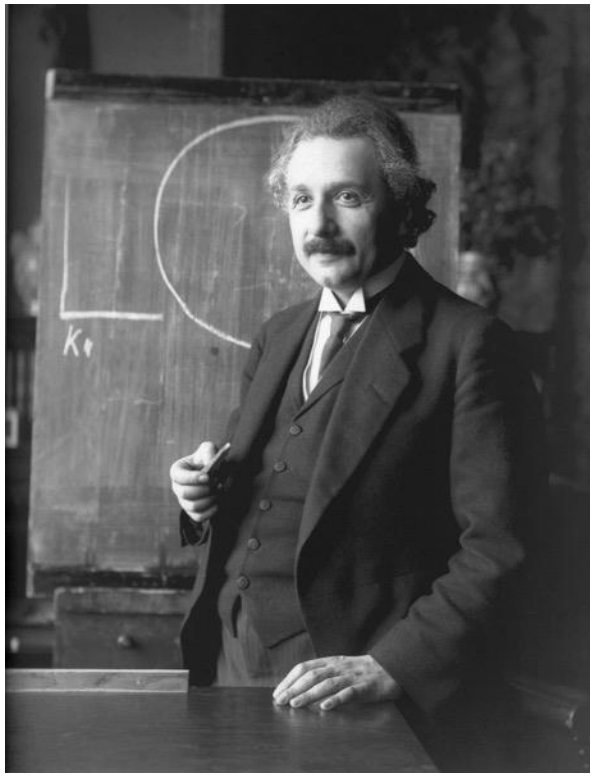
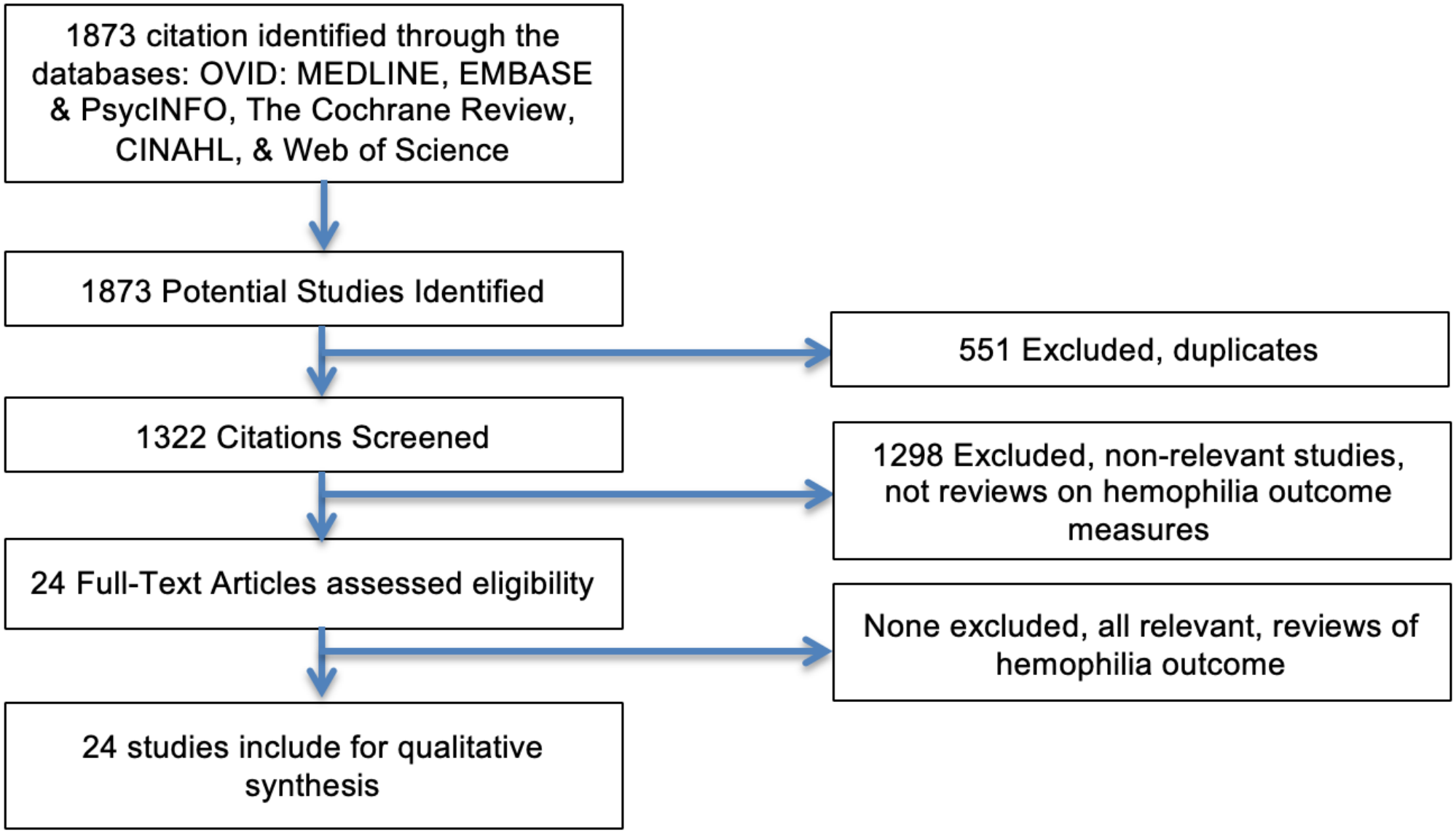
Are We Collecting the Right Data?



"Not everything that can be counted counts.
Not everything that counts can be counted."

Attributed to Albert Einstein
German-born theoretical physicist
1879-1955

Figure 1: Flow diagram of search results



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Current Primary Outcomes - Evidence

- 24 systematic reviews
  - published between 2002 and 2019
- Outcomes were grouped in 6 domains
    - bleeding;
    - HRQoL;
    - physical status, function, participation;
    - cost and resource use;
    - mortality and comorbidities.

- Outcomes were
  - adopted in >25 interventional clinical trials and hundreds of observational studies.
  - 39 hard clinical outcomes,
  - 21 surrogate,
  - 58 PRO
- Health Related Quality of Life
  - 56 measures
    - both generic and disease-specific tools.

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Table 2: Domains and number of associated outcomes found	
Domain	**Number of Associated Outcomes, n (%)**
Health Related Quality of Life (HRQoL)	38 (33.6)
Co-morbidity and Mortality	16 (14.2)
Assessment of Physical Status, Function and Participation	16 (14.2)
Bleeding and Homeostasis	15 (13.3)
Joint Assessment	14 (12.4)
Economic and Pharmacoeconomic Endpoints	14 (12.4)
TOTAL Number of Outcomes	113

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Current Primary Outcomes - Limitations

- Most outcomes, including bleeding, would require blinding for proper assessment, which is rarely done in hemophilia trials.
- The rate of acute joint bleeds varies from patient to patient and would suggest using a cross-over design for these trials.
- The development of long-term joint damage would require long observation of trial participants.
- Finally, the assessment of QoL is confounded by the disability paradigm.

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It is clear that although there have been great advances …, more needs to be done not only to develop new therapies …, but to address broader economic, social, and educational barriers that still remain.

Conclusion FDA Voice of the Patient Report
Hemophilia A/B, VWD and Other Heritable Bleeding Disorders.
May 2016

FDA

FDA Patient-Focused Drug Development Initiative Voice of the Patient Series Report on Hemophilia A/B, VWD, and Other Heritable Bleeding Disorders. May 2016

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PROBE

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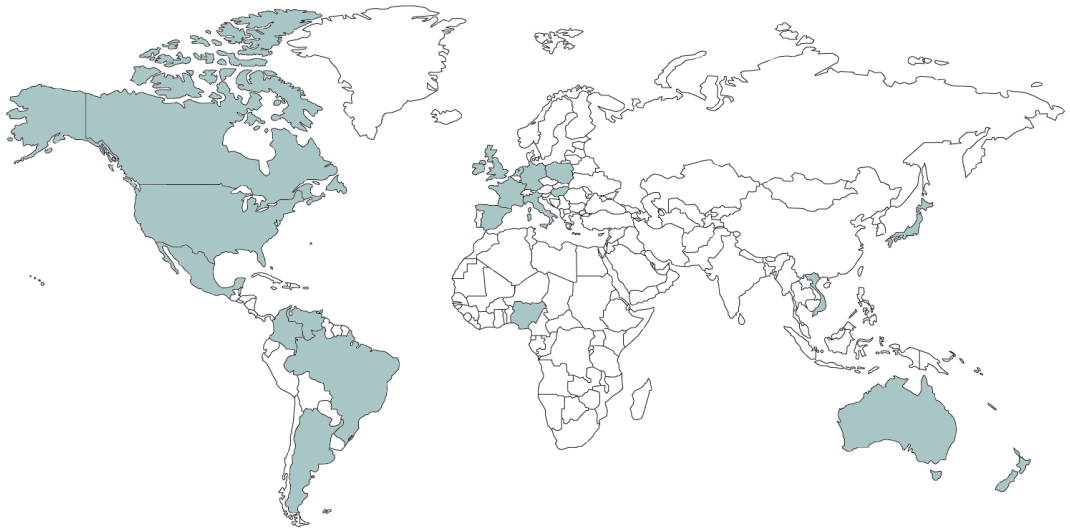
Collecting data on outcomes patient's deem relevant

- **Pain** - chronic/acute, interference, occurrence
- **Independence** - limitations, impact on activities of daily living
- **Education** - attainment, attendance
- **Employment** - duration, underemployment, attendance
- **Family life** - marriage, children
- **Mobility** - assistance required, impairment
- Current health status (EQ-5D-5L – VAS)

For patients, it also collects explanatory variables e.g., demographics, personal characteristics, treatment history, disease severity

PROBE Network / Questionnaire Project

- PROBE collects data on outcomes patient's deem relevant to their life
  - Comparator data from those not personally effected with a bleeding disorder
- 2,101 surveys from 24 countries
  - Collected 4/2015 - 2/2017
- PROBE questionnaire comprised of 4 sections
  - demographic data
  - general health problems
  - hemophilia-related health problems
  - health-related quality of life



Clinical Trial registration: NCT02439710

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Publications

- 4 manuscripts published
- 25 abstracts accepted at scientific meetings
  - ASH
  - EAHAD
  - ECRD
  - EHC
  - HTAi
  - ISTH
  - NHF
  - WFH
- 8 selected for oral presentation

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Global Footprint - Languages / Countries*

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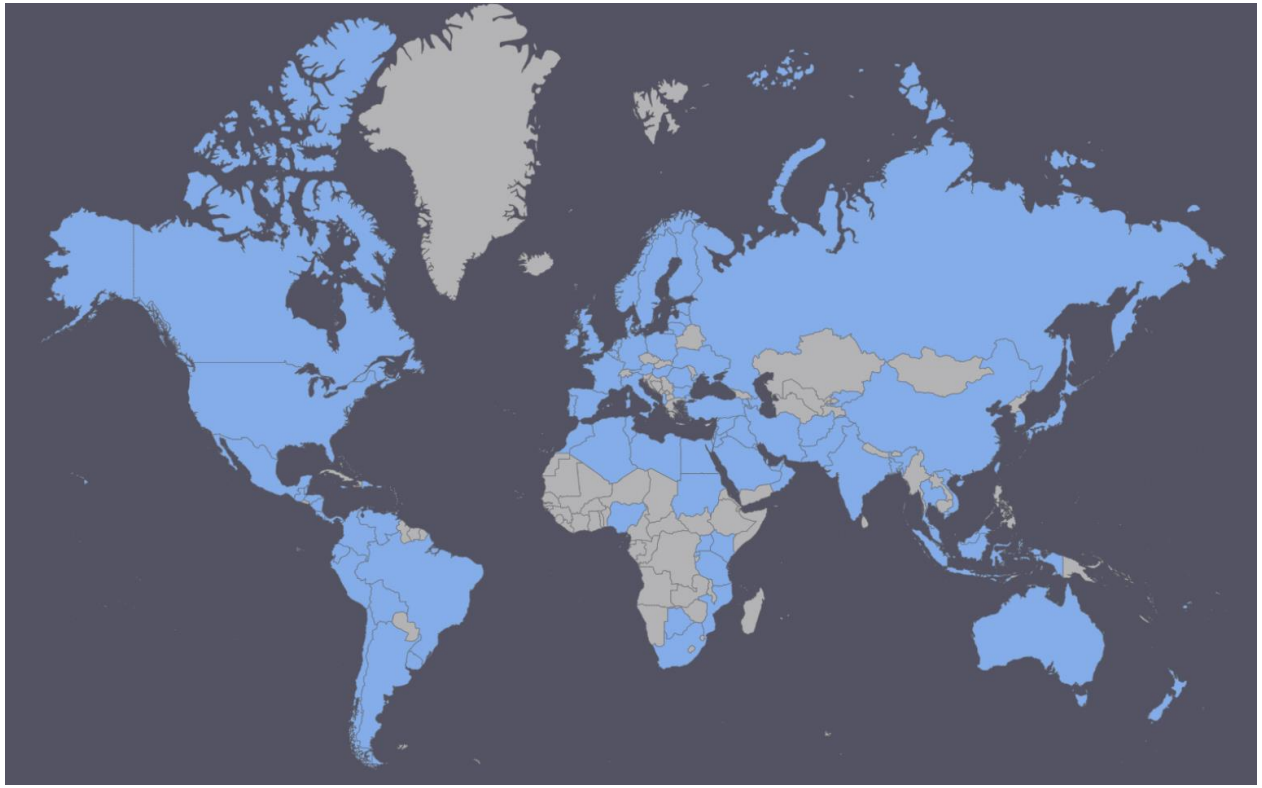
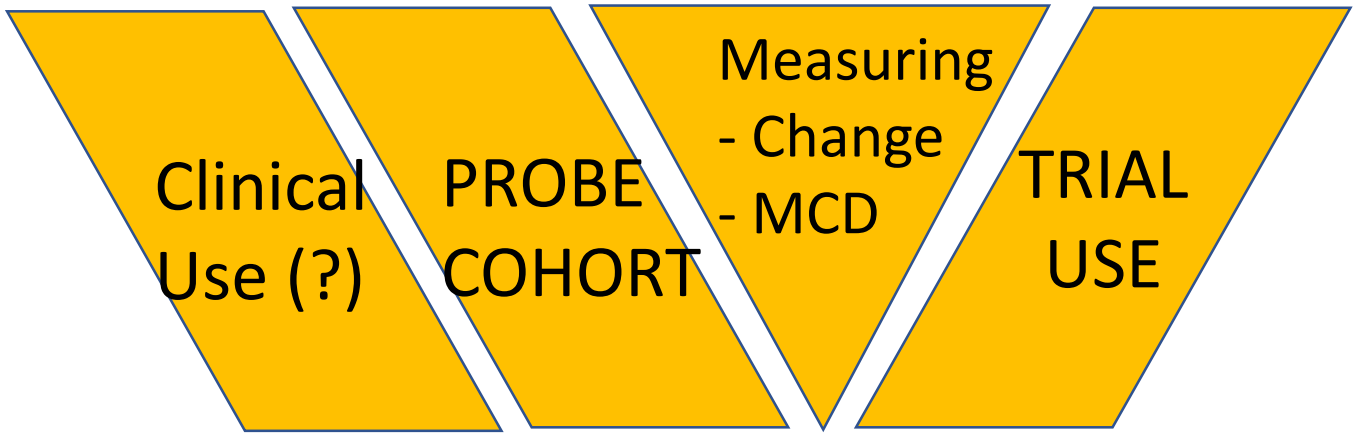
- Afrikaans
- Albanian
- Arabic (modern std.)
- Armenian
- Azerbaijani
- Bulgarian
- Chinese (simplified)
- Chinese (traditional)
- Danish
- Dutch
- English
- Estonian
- Farsi
- Finnish
- French
- German
- Hebrew
- Hindi
- Hungarian
- Italian
- Japanese
- Korean
- Kyrgyz
- Latvian
- Lithuanian
- Norwegian
- Polish
- Portuguese
- Punjabi
- Russian
- Sesotho
- Sotho
- Spanish
- Swedish
- Thai
- Ukrainian
- Vietnamese
- Xhosa
- Zulu



*Existing / In development



CORE PRO QUESTIONS & SUMMARY SCORE

Non-hemophilia norm data

Benchmark and normative data from a range of countries

ClinicalTrials.gov Identifier: NCT03549858.

PROBE®

Patient Reported Outcomes Burdens and Experiences Study

New Survey

Select your country and language to begin a new survey.

Country Please Select

Language Please Select

Begin »

Log in

OR

Enter your PIN to continue a previously started survey.
(You will get a PIN on the first page of a New Survey)

PIN

Resume »

Currently, HFA is only supporting the collection of fully anonymized data.

Please use the "Continue as guest option" below.

Haemophilia Foundation Australia

Haemophilia Foundation Australia (HFA) is the national peak body that represents the Australian bleeding disorders community. We are committed to improving treatment and care through representation and advocacy, education and the promotion of research. HFA works with a network of State and Territory Foundations to ensure everyone with bleeding disorders in Australia has access to the world's best practice treatment and care.

Should you have any questions about the survey, please contact hfaust@haemophilia.org.au

EXPLANATORY STATEMENT (Participant copy)

MUHREC Project Number: CF15/4363 - 2015001518

Australian Study Team
PROBE Team Australia Leader:
Suzanne O'Callaghan
Haemophilia Foundation Australia
Phone : 1800 807 173
Email: socallaghan@haemophilia.org.au

Monash University Chief Investigator:
Dr Liz Bishop
Michael Kirby Centre for Public Health
and
Human Rights, Monash University
Phone: 03 9903 0344
Email: liz.bishop@monash.edu

You are invited to take part in this study. Please read this Explanatory Statement in full before deciding whether or not to participate in this research. If you would like further information regarding any aspect of this project, you are encouraged to contact the researchers via the phone numbers or email addresses listed above.

Haemophilia Foundation Australia (HFA) and the Patient Reported Outcomes Burdens and Experiences

Registration Options

Register using MyCBDR

This links your PROBE data to your CBDR record. Contribute to research. See your changes over time.

Already linked your account? Login here

OR

Register using PROBE

For non-MyCBDR users and people who don't have a bleeding disorder. Contribute to research. See your changes over time.

Already have an account? Login here

OR

Continue as a guest

For one-time use.

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CHRONIC PAIN

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Pain and Hemophilia

- 89% of adults with hemophilia state that pain interferes with their lives
- Pain may impact physical health, well being and social engagement.
- Therefore, pain is a critical aspect of hemophilia.
- However, to date, there was no standardized pain measurement in people living with hemophilia.

Garrido C, et al. Hemophilia. 2012;18:177.
Rambod et al. Int J Community Based Nurs Midwifery. 2016 ; 4(4): 309–319.

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PROBE items on pain assessment

During the past 12 months, have you experienced or chronic pain?

If yes, when did your chronic pain occur? (Please check all that apply)

- ☐ Walking
- ☐ Stair climbing
- ☐ Nighttime (such as waking you up/keeping you awake)
- ☐ Resting
- ☐ Weight bearing
- ☐ Playing (including playing with children) or participating in sports / exercising
- ☐ After falling or a trauma
- ☐ Other (Describe): _____

If yes, when did your chronic pain occur? (Please check all that apply)

- ☐ General activity
- ☐ Mood
- ☐ Walking ability
- ☐ Normal work (including both work outside the home and housework)
- ☐ Attending school
- ☐ Relations with others
- ☐ Sleep
- ☐ Enjoyment of life
- ☐ Playing (including playing with children) or participating in sports / exercising
- ☐ Lifting
- ☐ Other (Describe): _____

(EQ-5D-5L)

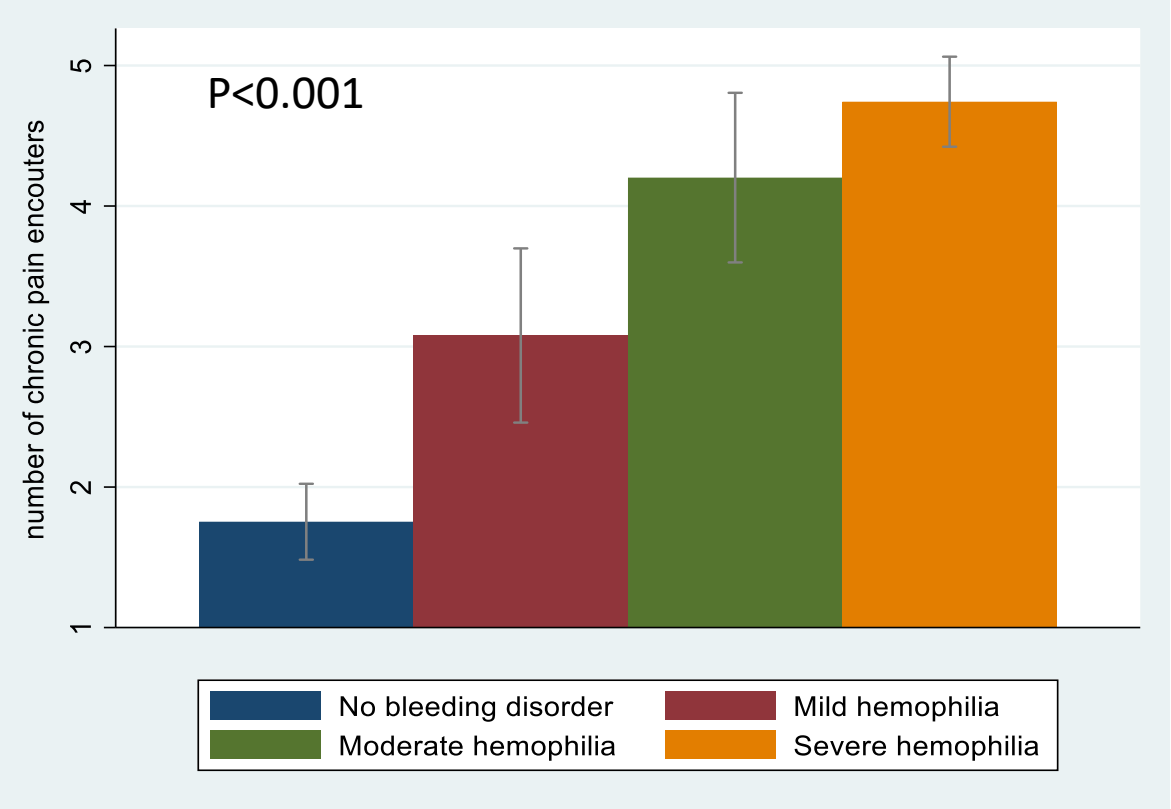
Under each heading, please check the ONE box that best describes your health TODAY.

PAIN / DISCOMFORT

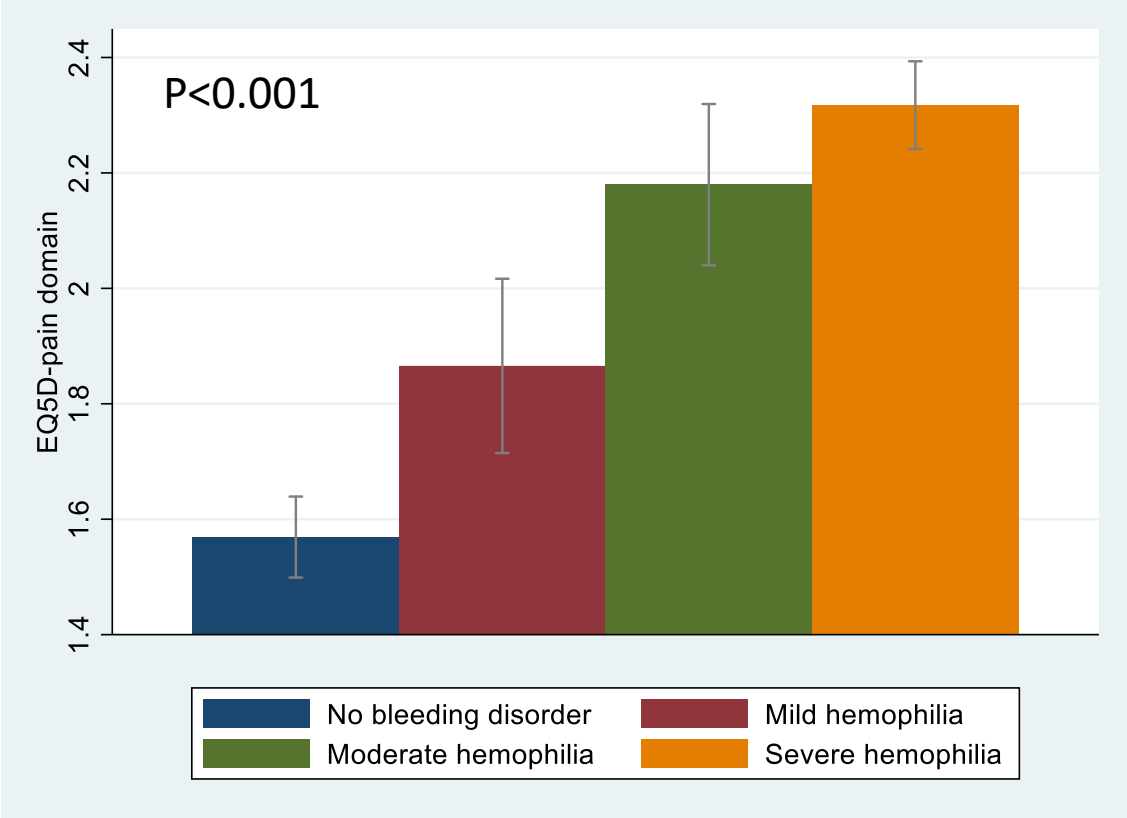
I have no pain or discomfort	❑
I have slight pain or discomfort	❑
I have moderate pain or discomfort	❑
I have severe pain or discomfort	❑
I have extreme pain or discomfort	❑

The mean number of chronic pain encounters assessed by the PROBE questionnaire

Mean number of chronic pain encounters



Mean pain utility score assessed by the EQ5D-5L



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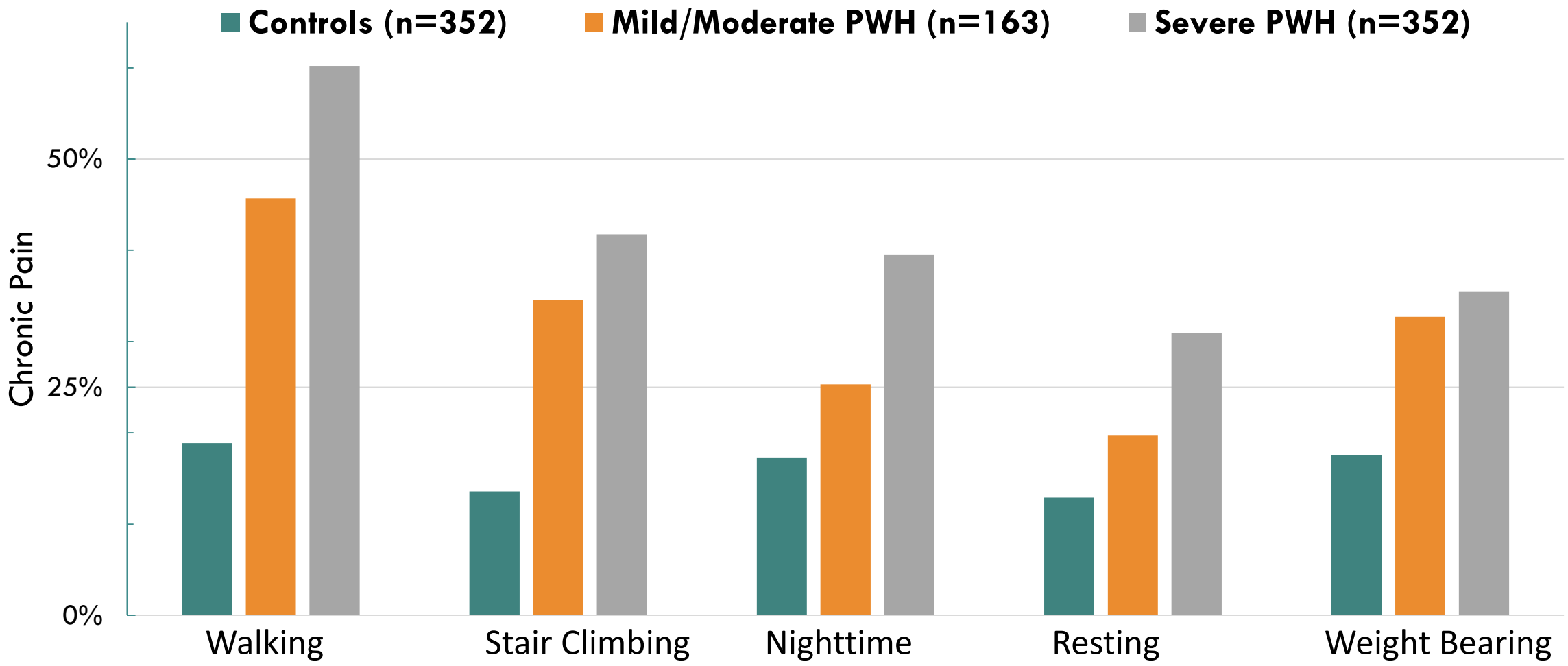
When chronic pain occurs



PROBE Investigators unpublished data not for citation

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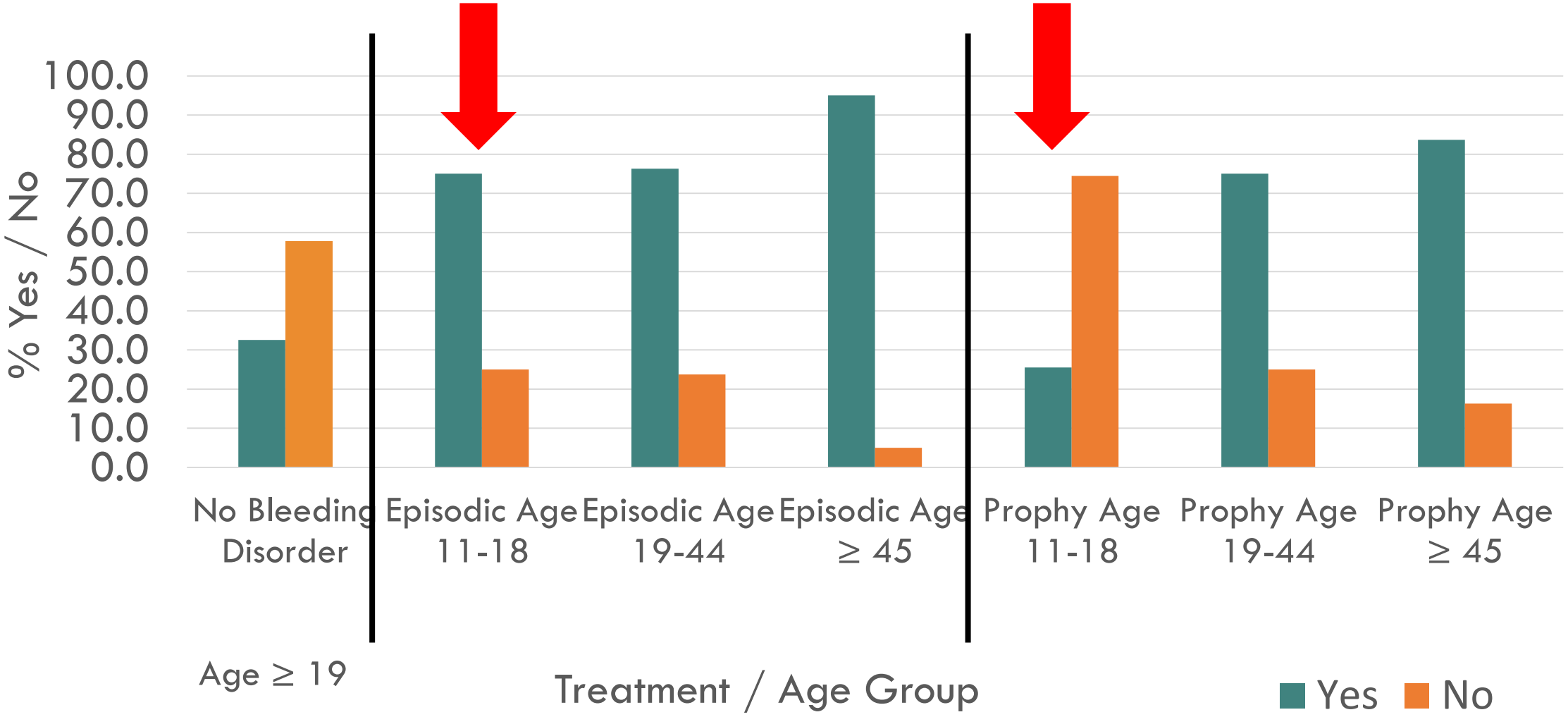
During the past 12 months have you experienced chronic pain?



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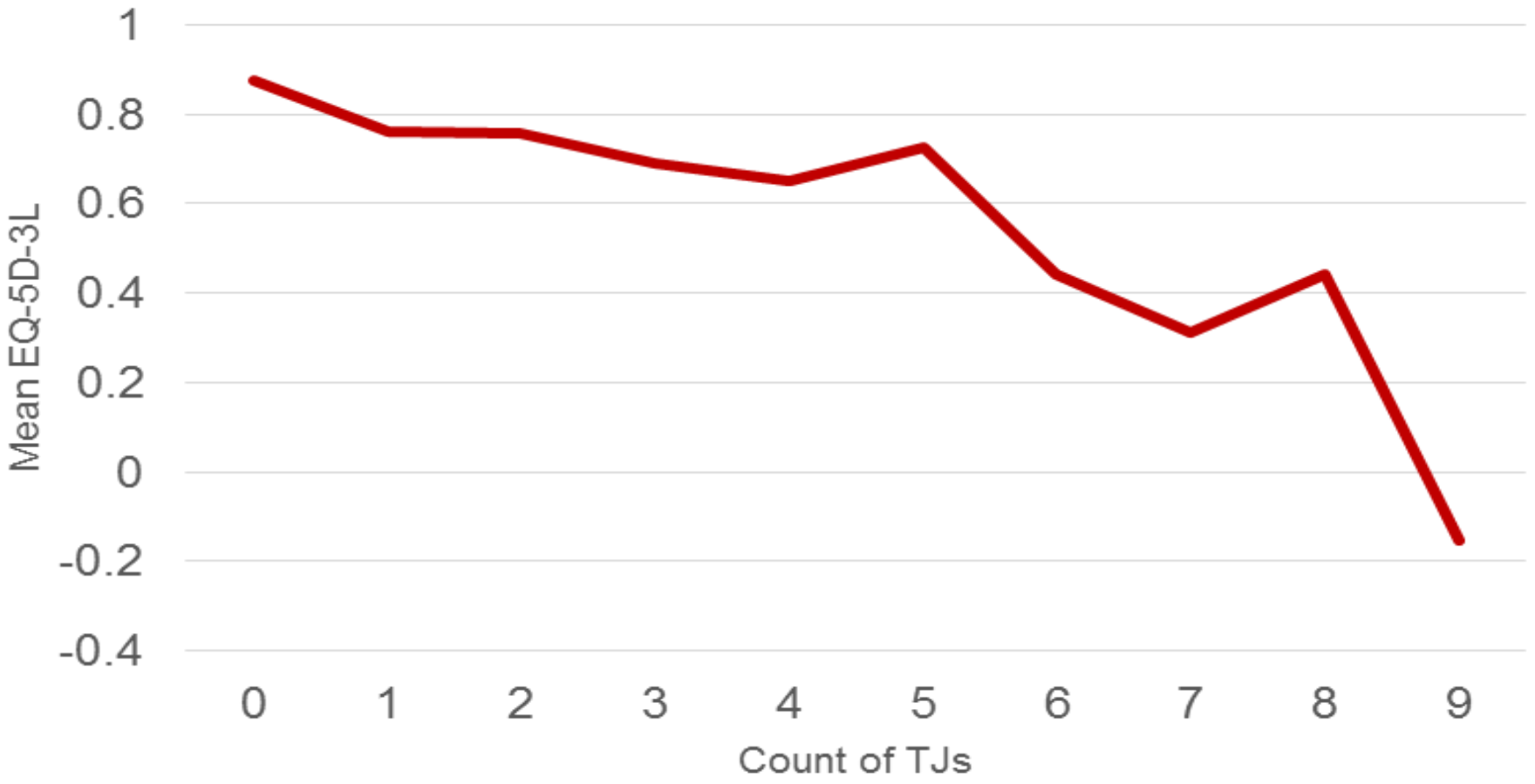
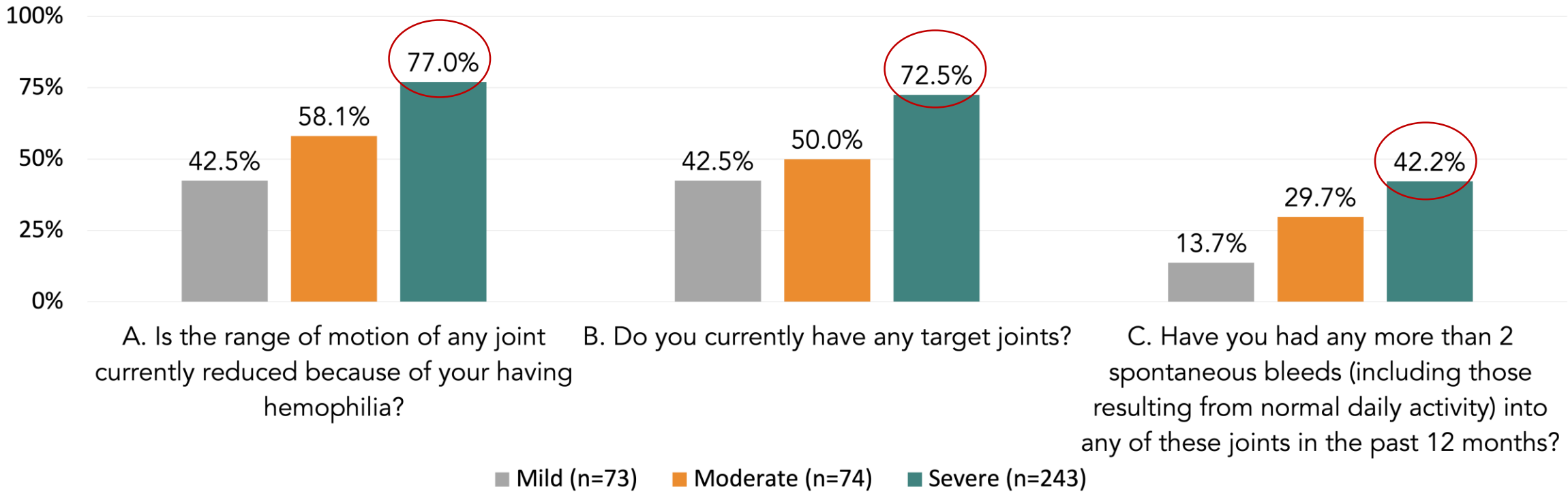
TARGET JOINTS

Impact of Severe Hemophilia and Presence of Target Joints on Health-Related Quality of Life



O'Hara et al. Health and Quality of Life Outcomes (2018) 16:84 DOI: 10.1186/s12955-018-0908-9; O'Hara et al. Health Economics Review (2018) 8:1 DOI: 10.1186/s13561-018-0185-7

Target Joints - Patient and Clinical Perspectives Differ



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Activities of daily living

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The effect of hemophilia on activities of daily living (ADL)

- The PROBE questionnaire asks a dedicated question to explore the impact of hemophilia on ADL, with 22 possible answers[1].

Do you <u>currently</u> have difficulty with any activities of daily living?

- ☐ *Yes*
- ☐ *No*

If yes, please check all that apply:

- ☐ Getting out of bed
- ☐ Bending down to the floor
- ☐ Putting on socks or shoes
- ☐ Getting up from sitting
- ☐ Getting on or off the toilet
- ☐ Taking a bath or shower
- ☐ Brushing or flossing teeth
- ☐ Grooming
- ☐ Going down stairs
- ☐ Sitting
- ☐ Getting in or out of the car
- ☐ Walking on a flat surface
- ☐ Shopping
- ☐ Lifting light items
- ☐ Standing without support
- ☐ Writing or using a computer
- ☐ Doing light domestic tasks
- ☐ Doing heavy domestic tasks
- ☐ Going up stairs
- ☐ Taking off socks or shoes
- ☐ Lying comfortably in bed
- ☐ Sexual intimacy
- ☐ Other (Describe): _____

PWH, people with hemophilia, ADL Activity of Daily Living; [1]Question #13 PROBE Questionnaire Version 2;

The effect of hemophilia on activities of daily living (ADL):

- Knowledge about the impact of hemophilia on activities of daily living is a critical component of a patient-centred approach to the management of this disease

	n	EQ-5D utility (range)	People reporting ADL being affected	Mean number of ADL affected per patient
No Bleeding Disorder	528	0.916 (0.905-0.926)	14.7%	0.75 (0.58-0.98)
Mild Haemophilia	109	0.849 (0.816-0.883)	30.6%	1.88 (1.11-2.64)
Moderate Haemophilia	129	0.773 (0.732-0.813)	60.9%	3.78 (2.94-4.62)
Severe Haemophilia	495	0.729 (0.708-0.751)	64.7%	4.87 (4.38-5.35)

Poster Presentation - European Conference On Rare Diseases And Orphan Product, May. 10-12, 2018, Vienna, Austria

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Conclusions

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Conclusions

- PROBE is a well calibrated instrument and correlates with EQ5D-5L.
- A field study is ongoing to assess correlation with other hemophilia specific instruments.
- The discriminative property of PROBE is found to be able to distinguish people with various severity of hemophilia as well as people without bleeding disorders.
- The responsiveness to change will be demonstrate going forward
- PROBE provided more informative data (more depth) than non specific instruments

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Conclusions

- The strength of the inference of data generated with PROBE depends on the study design, as for any PRO
- We have pivotal experience of PROBE performance for clinical trials
- We have just started assessing if it can have a role in the clinic, either as a stand alone or as a longitudinal assessment
- As a benchmark instrument for the assessment of real world data collections, PROBE is providing unparallel properties in the field
- We encourage investigators and clinicians to evaluate non-severe hemophilic patients using a patient-reported outcome assessing tool.

Acknowledgments

Investigators

- Mark Skinner JD, Institute for Policy Advancement Ltd. (US)
- Randall Curtis MBA, Factor VIII Computing (US)
- Neil Frick MS, National Hemophilia Foundation (US)
- Alfonso Iorio MD Ph.D. FRCPC, McMaster University (Canada)
- Michael Nichol Ph.D., University of Southern California (US)
- Declan Noone, Irish Haemophilia Society (Ireland)
- Brian O'Mahony, Irish Haemophilia Society, Trinity College Dublin (Ireland)
- David Page, Canadian Hemophilia Society (Canada)
- Jeff Stonebraker Ph.D., North Carolina State University (US)

Funders

- PROBE is an independent investigator led research project with grant / research support from:
  - Bayer Healthcare
  - Bioverativ, a Sanofi company
  - CSL Behring
  - Novo Nordisk
  - Roche
  - Shire
  - Sobi
- Collaboration of the US National Hemophilia Foundation and McMaster