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Current Controversies in Rare Diseases and Evidence-Based Advocacy

ISPOR Rare Disease Special Interest Group Forum

Virtual ISPOR Europe 2021

2nd December 2021

Panelists

Moderator:

- **Jamie O'Hara**: CEO, HCD Economics, UK

Speakers:

- **Sheela Upadhyaya**: Rare Disease & RAPID C-19 Strategic Advisor, NICE, UK
- **Brian O Mahony**: CEO, Irish Haemophilia Society; Ireland
- **Mohit Jain**: Vice President Market Access EMEA, Biomarin, UK
- **Persefoni Kritikou**: RWE Manager, HCD Economics, UK

Agenda

- SECTION 1
  - Introduction to the SIG – Jamie
- SECTION 2 – Consultation Process
  - Rationale & Description of the Consultation Process – Sheela
  - Equity – Sheela
  - Evidence-Based Advocacy – Brian
  - Regulatory Process – Brian
  - Health Economic Evaluation – Mohit
  - Data Collection Process – Mohit
- SECTION 3 – Key Project
  - Key Project on Evidence-Based Advocacy – Persefoni
- Q&A - Jamie

SECTION

1

Introduction to the SIG

Introduction to the ISPOR Rare Disease Special Interest Group (SIG)

Rare Disease

Special Interest Group

Mission

To identify issues in the rare disease environment so that all stakeholders can effectively address key challenges and more effectively establish the value of new and existing diagnostics and therapeutics.

Background

Rare disease is a rapidly expanding area of research and clinical development. Advancements in genetic understanding and other scientific breakthroughs have led to improved identification of rare conditions and possible pathways for improving rare disease diagnosis and treatment, as well as stratifying relatively common diseases into many rarer ones.

As clinicians are better able to diagnose specific rare diseases, new treatments are becoming available for clinical development. However, treatments for rare diseases are typically available at much higher "per patient" cost, which (along with other factors) create challenges to payers, providers and patients.

The ISPOR Rare Disease SIG Mission and Vision

Our **Mission** is to identify the areas that warrant further attention in the space of Rare Diseases, across five main key areas: equity implementation, evidence-based advocacy, regulatory process, health economic evaluation and data collection process

Our **Vision** is to be able to generate recommendations for future directions in the Rare Disease space, as they relate to the ISPOR strategy

Key Milestones in Rare Diseases

1972
Outline of Measures to Combat Intractable Diseases in Japan

1983
The Orphan Drug Act in the US

1997

1998
Orphan Drug Program in Australia

2002
The Rare Disease Act in the US

2011

2017

2018
THE UK STRATEGY FOR RARE DISEASES

2020
Health Canada Special Access Program

Ongoing Discussions in Rare Diseases

What is the societal view on genetic predisposition vs bad life choices?

To what extent is the rare disease patient voice heard?

Is the social insurance contract met in the space of rare diseases?

How does the disability paradox in rare diseases affect access to new treatments?

What are the society's perception towards payers and pharmaceutical industry when innovative but expensive drugs are denied reimbursement?

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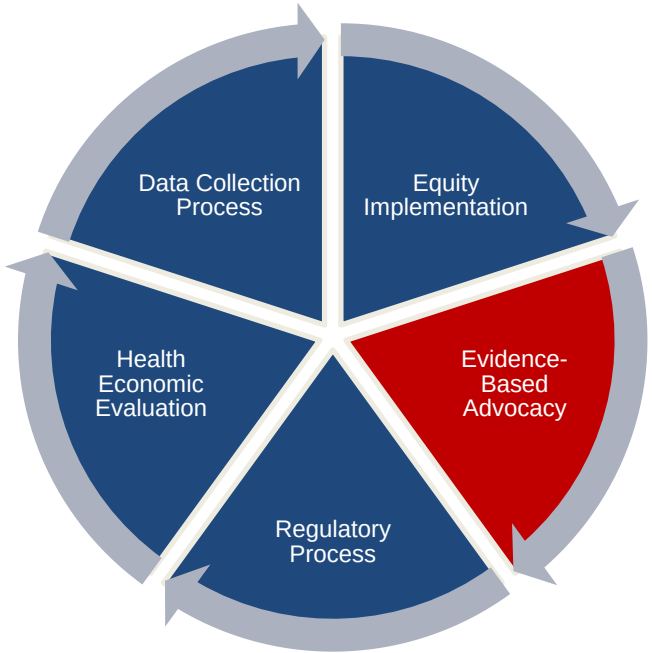
Consultation Process

Rationale for the Consultation Process

In order to define the future strategic directions of the ISPOR Rare Disease SIG, we performed a consultation process with Rare Disease Experts across 5 key areas.



Description of the Consultation Process

Selection of Participants

- Rare disease experts with various professional backgrounds
- Representation across different geographies

Interview Process

- One-hour video calls
- Information sheet describing the aims of the consultation process sent in advanced
- Informed consent for use of information at an aggregate level was sought

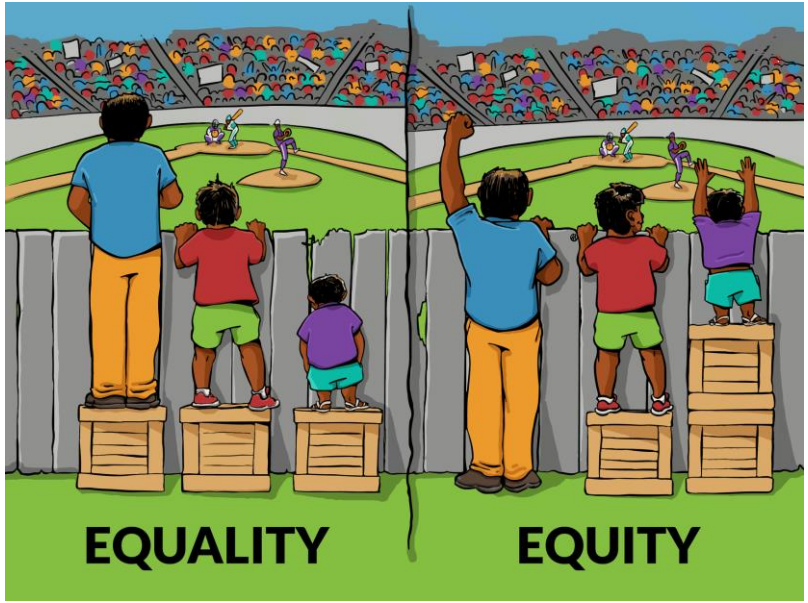
Interview Content

Key Definitions: Equity & Evidence-Based Advocacy

Current practices, unmet needs and future directions:

- **Equity Implementation**
- **Evidence-Based Advocacy**
- **Regulatory Process**
- **Health Economic Evaluation**
- **Data Collection**

Definition of ‘Equity’



Source: Interaction Institute for Social Change | Artist: Angus Maguire [1]

EQUITY: “The situation in which everyone is treated fairly and equally”

Cambridge Advanced Learner's Dictionary & Thesaurus

HEALTH EQUITY: “Equity is the absence of unfair, avoidable or remediable differences among groups of people, whether those groups are defined socially, economically, demographically, or geographically or by other dimensions of inequality (e.g. sex, gender, ethnicity, disability, or sexual orientation). Health is a fundamental human right. **Health equity is achieved when everyone can attain their full potential for health and well-being”.**

World Health Organization (WHO) [2]

Poll Question 1

To what extent do you feel that **Equity** is currently implemented in the provision of care for people affected with **Rare Diseases**?

- Only minimally
- To a small extent, under specific circumstances
- To a sufficient extent
- To a great extent, covering almost all cases for Rare Diseases

Consultation Process Outcomes : Equity

*We need to define what we mean by equity – **a value-based system** where trade-offs between different diseases are made, or **a humanistic system** where all patients with marginal benefits should be treated?*

*Rare disease therapies are a fragmented world, but we need to **finance and develop rare disease drugs centrally**, to allow economies of scale*

*Current healthcare systems are designed such that everybody receives the same care initially but without accounting for future differentiation based on disease severity. **Need to start at reforming primary care to allow easier access to a specialist/ reference centres.***

"Incentives heavily weighted towards communities that could pay for the relevant research, leaving behind areas with no funding opportunities"

HTA agency

"Geographical differences are also very evident – depending on where you are born you die, or you live if you have muscular dystrophy."

Patient Association

Definition of ‘Evidence-Based Advocacy’

“Use of verified concrete information as proof to trigger change”

Advocacy using reasoned argument based on best attainable evidence-based data and experiential data, utilizing patient-relevant outcomes, including real-world experience and case studies

PROBE®
Patient Reported Outcomes Burdens and Experiences Study

Consultation Process Outcomes : Evidence-Based Advocacy

EBA should be integrated across the whole spectrum of rare diseases: equity implementation, regulatory process, health economic evaluation, and data collection process

Translating the patient-provided information into metrics *that can be included in the decision-making process*

Capture the patient and caregiver perspective outside the healthcare visits, as experienced ***7 days per week***

Transform the healthcare system to enable the people affected with rare diseases to ***maneuver through the various settings***

"The naïve patient in rare diseases and in cancer is a dead patient"
Patient Association

"Evidence has to guide everything"
Patient Association

"There has been an important shift from patients being objects of medical interventions, to them being subjects"
Academia

The Patient Advocacy Group Perspective on the Implementation of Evidence-Based Advocacy

For rare diseases, randomised control trials not usually feasible

RCTs not the appropriate standard to apply to rare diseases

PAGs can collaborate with health care professionals in the collection of clinical data and can also separately collect QOL and experiential data

Proactive planning of data and evidence collection before a treatment commences allows for impact of treatment to be measured

Validated quality of life tools, surveys, focusing on PROs

Importance of qualitative data often overlooked- focus groups

A Value Framework Example in Haemophilia

	Key Findings	Evidence Favoring Prophylaxis
Tier 1: Health Status	Prophylaxis favored over on-demand therapy in outcomes of bleeding, musculoskeletal complications, pain, function/activity, and QOL	↓ Missed activities and work/school days [a,b] ↓ Annual bleed rate and joint bleeds [b-g] ↓ Life-threatening/trauma-related bleeds [c-g] ↓ Intracranial hemorrhage [h] ↓ Pain [g,i,j] ↓ Joint damage/target joint development [b-d,k] ↑ HRQOL [b,d,g] *No direct comparisons for survival
Tier 2: Recovery	Prophylaxis favored in measures of recovery time, return to normal activities, orthopaedic intervention, and venous access	↓ Missed activities and work/school days [a,b] ↓ Joint-related surgeries [i,j] *No differences in inhibitor development [b-e,g]; greater risk of infections from indwelling catheters with prophylaxis [d,l]
Tier 3: Sustainability	Prophylaxis favored in measures of breakthrough bleeds, joint preservation, sustained productivity, and QOL	↓ Recurrent or spontaneous bleeds [e-g,i] ↓ Development of arthropathy [c,d] ↑ Normal joint structure [c] ↑ Academic achievement scores [m] ↑ Physical/recreational activity [n] ↑ HRQOL over time [d,n] *Improvement in arthropathy not shown with secondary prophylaxis[l]; data on long-term consequences of therapy NA

[a] Noone et al. Haemophilia 2013;19:44; [b] Tagliaferri et al. J Thromb Haemost 2015; 114:35; [c] Manco-Johnson et al. NEJM 2007; 357:535; [d] Gringeri et al. J Thromb.Haemost 2011; 9:700; [e] Manco-Johnson et al. J Thromb Haemost 2013; 11:1119; [f] Kavakli et al. J Thromb Haemost 2015; 13:360; [g] Valentino et al. J Thromb Haemost 2012; 10:359; [h] Witmer et al. BJH 2011; 152:211; [i] Noone et al. . Haemophilia 2011; 17:e831; [j] Pocoski et al. Haemophilia 2015; 21:14–94; [k] Aledort et al. J. Intern Med 1994; 236:391; [l] Manco-Johnson. Haemophilia 2007; 13:4; [m] Shapiro et al. Pediatrics 2001; 108:E105; [n] Hong et al. Haemophilia 2014; 20:1–186.


ORIGINAL ARTICLE

WILEY Haemophilia

Patient-centred value framework for haemophilia

B. O'Mahony[1] | G. Dolan[2] | D. Nugent[3] | C. Goodman[4] | on behalf of the International Haemophilia Access Strategy Council


ORIGINAL ARTICLE

WILEY Haemophilia

Value of prophylaxis vs on-demand treatment: Application of a value framework in hemophilia

Diane Nugent[1] | Brian O'Mahony[2] | Gerry Dolan[3] | on behalf of the International Haemophilia Access Strategy Council

Experiential Data: PAGs Collaboration

Country	Bleeds p.a.	Days missed	QOL
Sweden	3.2	0.5	1
UK	17.5	6.6	0.73
Ireland	16.5	5	0.76
France	20.1	15	0.73
Poland	30		0.63

Young men from 20-35 years
Sweden – always treated preventatively [a]


Prophylactic treatment in an adult patient with severe hemophilia – effectiveness and costs

German Hemophilia Society[1], HELIOS Klinikum Erfurt, Germany[2]

[1]St. Schlenkrich, [2]Ch. Schubert

Introduction:

Case report:

Results:

Conclusions:

References:

Year on preventive treatment: 16% increase in therapy use resulted in 86% decrease in bleeding episodes and 84% decrease in days missed at work [b]

[a] Noone, O'Mahony, et al. Haemophilia 2020; [b] Schlenkrich S et al, Haemostasologie

Identifying what's important to patients

Patient Preferences and Priorities for Haemophilia Gene Therapy in the US: A Discrete Choice Experiment

Michelle Witkop[1], George Morgan[2], Jamie O'Hara[2,3], Michael Recht[4,5], Tyler W. Buckner[6], Diane Nugent[7], Randall Curtis[8], Brian O'Mahony[9,10], Mark W. Skinner[11,12], Brendan Mulhern[13], Matthew Cawson[2], Talaha M Ali[14], Eileen K Sawyer[14], Nanxin Li[14]

[1]National Hemophilia Foundation, New York, NY, USA; [2]HCD Economics, Daresbury, UK; [3]Faculty of Health and Social Care, University of Chester, Chester, UK; [4]Oregon Health & Science University, Portland, OR, USA; [5]American Thrombosis & Hemostasis Network, Rochester, NY, USA; [6]Hemophilia and Thrombosis Center, University of Colorado School of Medicine, Aurora, CO, USA; [7]Depa
UK; [10]Trinity College, Dublin, UK; [11]Institute for Policy Advancement, Ltd., V

INTRODUCTION

- Persistent bleeding and associated sequelae impose significant limitations on the daily functionality, mental health, and quality of life for people with moderate or severe haemophilia (PWH).[1,2]
- Gene therapy has shown promise in clinical trials for patients with haemophilia A or B, making long-term functional remediation of haemophilia a potential reality.[3-5]
- To date, patient preference studies in haemophilia have focused on the attributes of factor replacement therapies, with preferences predominantly related to efficacy, inhibitor development, and treatment administration.[6-8]
- Few studies have attempted to quantify patient preferences related to gene therapy attributes, and none of those exploring this emerging area have applied a discrete choice experiment design among patients with moderate or severe haemophilia A or B.[9,10]

AIMS

- To examine treatment preferences, including gene therapies, of PWH using a discrete choice experiment (DCE).
- To explore whether differences in preferences were identified by haemophilia type.

METHODS

- A DCE was completed by
  Health State Utility Value
  November-to-February 2
- A systematic literature re
  attributes and previous p
  in haemophilia, were und
  structured interviews with
  clinical experts to popula
  levels.
- The attributes and levels
  presented in Table 1.
- Each participant complete
  selecting their preferred c
  pairs of treatment scenar
  levels.
- Dominated scenarios we
  inconsistencies in respon
  failed these scenarios we
  analysis.
- Descriptive summary of c
  information was conducte
- Conditional logit models
  limitations, other modellin
  logit was used as the prin
- Analyses were conducte
  importance given to each
- Data for PWH was analy

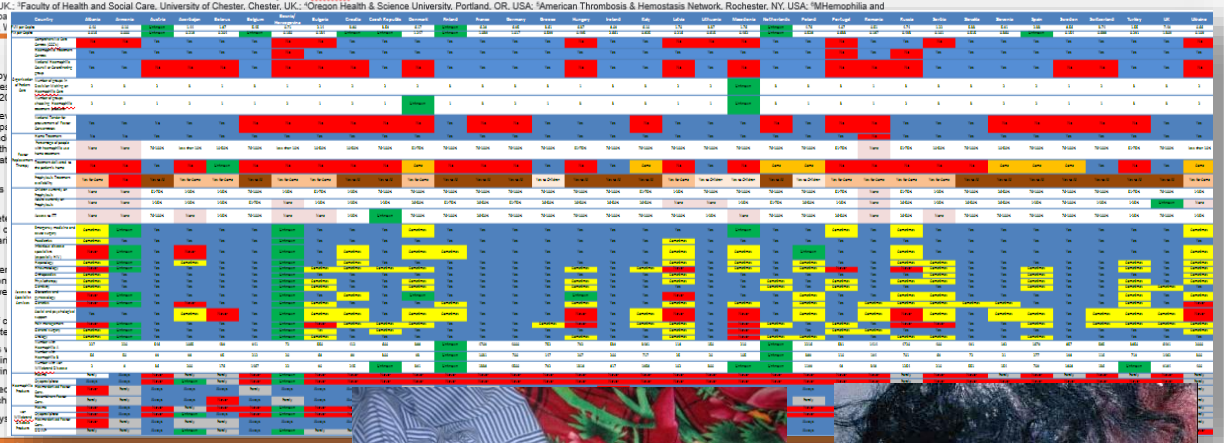
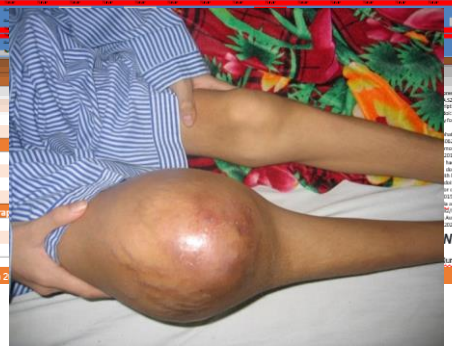


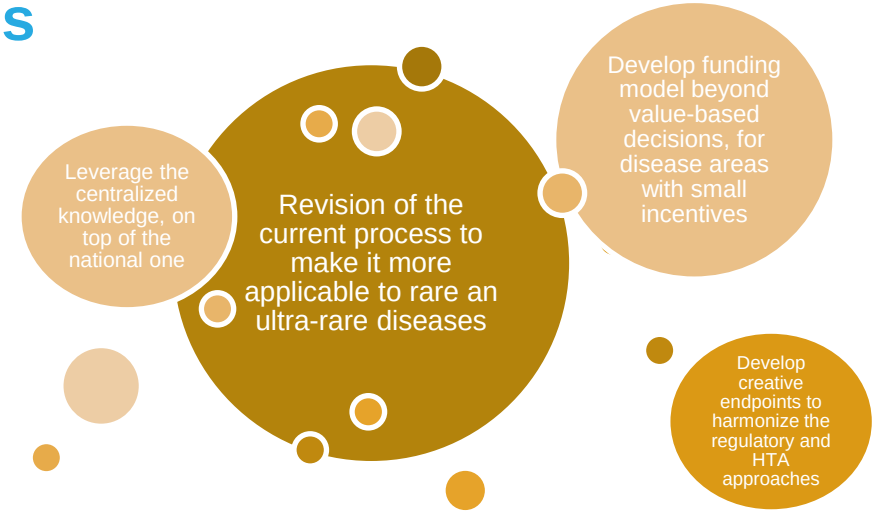
Table 1:Attribute and levels used in the DCE design A or B .

Attributes and Levels	
Dose frequency and durability	**Effect on overall annual bleeding rate**
Administration multiple times per week	*0 bleeds per year*
Administration every 1-4 weeks	*1 bleed per year*
One-time treatment, 10-year durability then return to standard of care at that time	*3 bleeds per year*
One-time treatment, lifetime durability	*5 or more bleeds per year*
Uncertainty regarding short-term or long-term significant safety issues	**Impact on activity of daily life/physical activity**
Very low risk of short-term OR long-term significant safety issue	*Freedom to undertake daily activities, travel, and physical activity*
Potential risk of short-term safety issue	*Some planning required to undertake daily activities, travel, and physical activity*
Potential risk of long-term safety issue	*A lot of planning required to undertake daily activities, travel, and physical activity*
Potential risk of short-term AND long-term significant safety issue	
Transformative/mental health impact	**Post treatment, possibility to undergo minor surgery without need for factor thera**
Freedom from thinking and worrying about haemophilia or the treatment most days	*Factor therapy generally NOT needed*
Thinking and worrying about haemophilia or the treatment some days	*Factor therapy may or may not be needed, depending on the situation*
Thinking and worrying about haemophilia or the treatment most days	*Factor therapy always needed*

Presented at the International Society on Thrombosis and Hemostasis (ISTH) 2



Consultation Process Outcomes : Regulatory Process



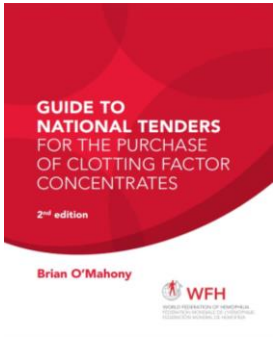
"Current processes are standardised, and the rare diseases need to adapt to these"
Patient Association

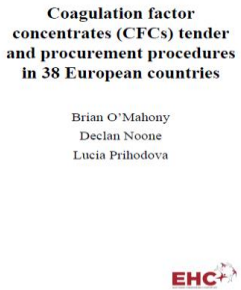
"It is quite frustrating to get regulatory approval but no reimbursement"
Pharma

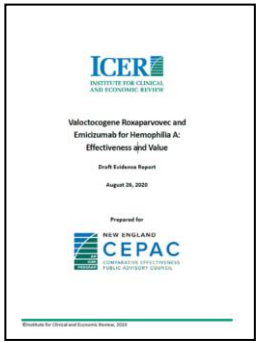
"With the increasing number of trials patients have more options on which one to join, and they usually prefer one that has no placebo arm"
Pharma

The Patient Advocacy Group Perspective on the Implementation of the Regulatory Process

- Need for different QALY limits for rare and ultra rare diseases
- Work with clinicians, payers and regulators to define optimal access and reimbursement methods for rare diseases
- Ensure the patient voice is formally included via the PAGs







"One interesting feature about hemophilia: It has one of the most organized and sophisticated patient groups, and they've spent a lot of time thinking about quality of life and how to create comprehensive measures of outcomes for patients. These patient groups will help fill in the gaps [in our assessments]".

Steve Pearson, ICER, USA 2021

Consultation Process Outcomes : Health Economic Evaluation

*Rare disease therapies often **deliver significant value for patients and society** that go beyond traditional HTA frameworks such as cost/QALY*

*Rare disease therapies **often have a more limited/uncertain evidence base** at the time of launch that cannot meet traditional evidence frameworks such as GRADE*

*Many rare disease therapies are **highly innovative**, meaning R&D costs can be high [3].*
*At the same time these therapies have **a limited patient population so** cost per patient can be high to cover the cost of investment*

"Cost effectiveness is a given, but we should also assess drugs in another level – e.g. rarity. QALYs are not designed for rare diseases"
Patient Association

"MCDA still not integrated"
HTA agency

"This again relates to equity and what is fair"
HTA agency

GRADE = Grading of Recommendations, Assessment, Development and Evaluation

The Industry Perspective on the Implementation of Health Economic Evaluation

There has been progress on the development of rare disease therapies in recent years, thanks in part to regulatory incentives [3] ,however ‘access’ remains a hurdle since HTA methods struggle to capture the full value of rare disease therapies [4]

Include totality of evidence (real world evidence, pragmatic trial designs, indirect comparable data, societal & patient evidence)

Formally integrate evidence-based advocacy and deliberation into HTA process decision making with transparency

Adopt broad-based approaches to health economics including elements of value beyond the healthcare perspective (e.g. disease severity, insurance value, equity, scientific spillovers etc…)

Consultation Process Outcomes : Data Collection Process

Developing treatments for rare diseases is more challenging and complex, than for common diseases [5]

Rare diseases

- ✓ Limited disease understanding and existing natural history data
- ✓ Limited number of experienced clinicians/specialised centres
- ✓ Challenges in diagnosis/identifying patients
- ✓ Small patient numbers and need to establish multiple clinical sites for only a few patients

Common diseases

- ✓ Often large body of evidence on disease and existing registries/natural history data
- ✓ Clinical experience
- ✓ Established diagnostic pathways
- ✓ Large patient numbers globally

"Heterogeneity is a huge issue around data collection in rare diseases"

Patient Association

"For rarer diseases the registries are unable to provide enough data"

Academia

"Patients not being treated in reference centers face different quality of care"

Pharma

The Industry Perspective on the Implementation of the Data Collection Process

Evidence-based advocacy and deliberation are critical in rare disease to fill some of the gaps

- Evidence-based advocacy can inform **broader methods of assessing value** to integrate the **patient perspective** providing important **insights** into the **disease burden and treatment value**
- Although evidence-based advocacy and deliberative processes are not new to HTAs, they are **not fully integrated** into HTA processes, there is a **need for more transparency, inclusivity and impartiality**
- **Important** to integrate methods for **data collection** to support evidence-based advocacy into **HTA processes**; e.g. Discrete Choice Experiments, patient surveys, disability paradox

3

Key Project: Evidence-Based Advocacy

The Importance of Patient Advocacy in Rare Diseases

The importance of the 'Patient Voice' has been widely recognized in the health care sector, and even more so in the case of Rare Diseases [6].

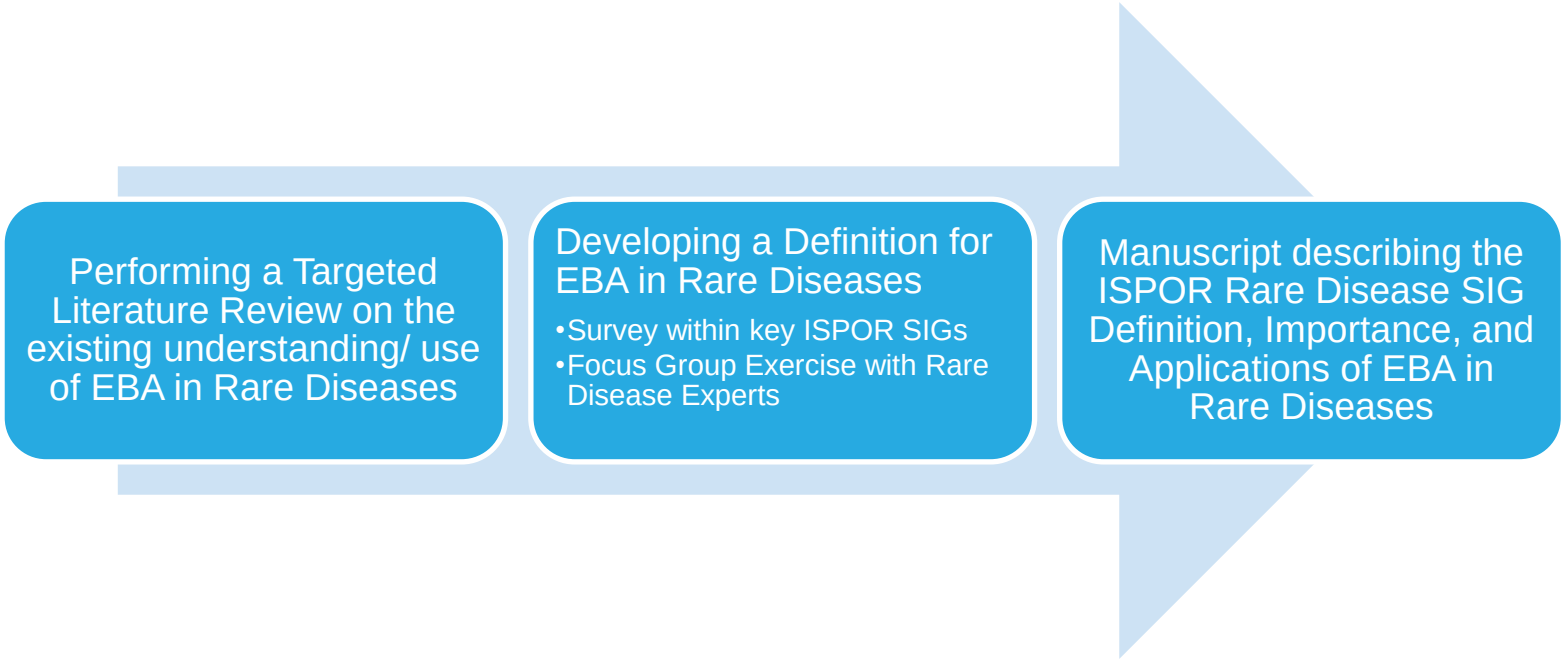
REGULATORY PROCESS
A common reason for inability to get regulatory and reimbursement approval for new rare disease medications is the lack of demonstration of improvement in meaningful health outcomes for patients [7,8].

HEALTH TECHNOLOGY ASSESSMENT
The uncertainty surrounding the HTA process in rare diseases (due to lack of sufficient and robust clinical data, or insufficient knowledge of the natural history of the disease) can only be mitigated throuh a collective approach, including clinical researchers, industry, HTA agencies, policy makers and patients [9].

Why a Key Project on Evidence-Based Advocacy is Needed

Background	• **Evidence-Based Medicine** and **Evidence-Based Reimbursement** have been well recognized and integrated into the regular medical/ economic practice. •There is **no consensus, however, on the definition and implementation of Evidence-Based Advocacy.**
Audience	•The audience for this project includes a **variety of stakeholders** in the rare disease area, ranging from Patient Advocacy Groups (PAGs), including caregivers; clinicians; the industry; regulatory authorities; health technology assessment bodies; health care decision makers; and health economic and outcomes research scientists
ISPOR Science Strategy	•**Patient-centered research** •**Special Population and Technologies**
Contribution to HEOR Science	•Develop a **consensus** on the definition of EBA in Rare Diseases, within the HEOR remit •Identify the **current use and importance** of EBA implementation across all HEOR tasks

Suggested Outline of the Key Project on Evidence-Based Advocacy



Next Steps

- Call for people to help!
- Please provide your comments to the chat box
- Let us know of any thoughts/ suggestions to the ISPOR Rare Disease SIG
  - Contact us at: rarediseasesig@ispor.org
  - Or contact Theresa Tesoro, MSN, Associate Director, Scientific and Health Policy Initiatives, at: ttesoro@ispor.org

4

Q&A

Poll Question 2

Which research area do you think the ISPOR Rare Disease SIG should prioritize in the future?

- **Incentivizing research**: suggestions for new funding models that better fit rare and ultra-rare diseases
- **Revision of regulatory processes for rare diseases**: e.g. developing a set of guidelines specific to rare diseases and especially for pediatric patients; or an addendum to the GDPR for rare diseases
- **Health policy issues**: suggestions for centralization of rare disease research and development, including the long-term effects of the introduction of innovative treatments
- **Review of data requirements**: combining clinical trials with synthetic data and real-world evidence for capturing prevalence
- **Economic evaluation of rare diseases**: integrating the social impact of the diseases, including the cost of not treating a person affected by a rare disease

Q&A Section

- Any Questions?

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- Let us know of any thoughts/ suggestions to the ISPOR Rare Disease SIG
  - Contact us at: rarediseasesig@ispor.org
  - Or contact Theresa Tesoro, MSN, Associate Director, Scientific and Health Policy Initiatives, at: ttesoro@ispor.org

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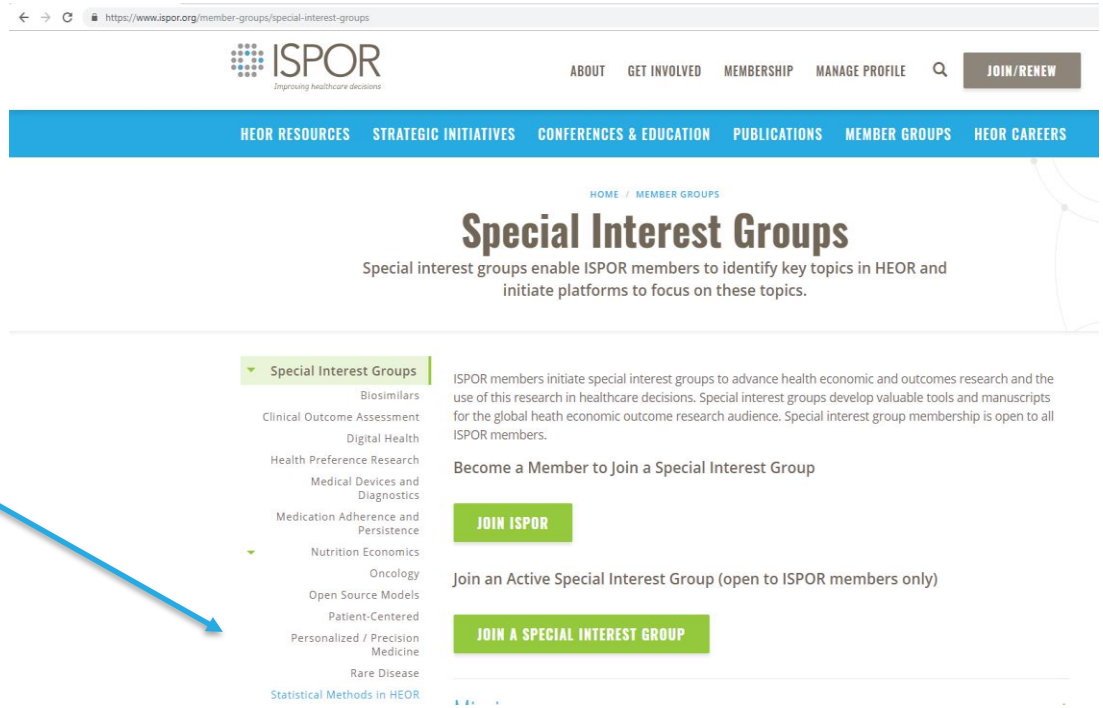
You must be an ISPOR member to join a Special Interest Group



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