Current Controversies in Rare Diseases and Evidence-Based Advocacy

ISPOR Rare Disease Special Interest Group Forum
Virtual ISPOR Europe 2021
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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
Introduction to the SIG
Introduction to the ISPOR Rare Disease Special Interest Group (SIG)

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: Orphan Drug Program in Australia
- 2002: The Rare Disease Act in the US
- 2011: Health Canada Special Access Program
- 2017: The Orphan Drug Program in Australia
- 2018: The Rare Disease Act in the US
- 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?
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 advance
• Informed consent for use of information at an aggregate level was sought

Interview Content

Current practices, unmet needs and future directions:
• Equity Implementation
• Evidence-Based Advocacy
• Regulatory Process
• Health Economic Evaluation
• Data Collection

Key Definitions:
Equity & Evidence-Based Advocacy
Definition of ‘Equity’

**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”

Patient Association

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

HTA agency
“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.
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.**

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

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

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

Experiential Data: PAGs Collaboration

<table>
<thead>
<tr>
<th>Country</th>
<th>Bleeds p.a.</th>
<th>Days missed</th>
<th>QOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sweden</td>
<td>3.2</td>
<td>0.5</td>
<td>1</td>
</tr>
<tr>
<td>UK</td>
<td>17.5</td>
<td>6.6</td>
<td>0.73</td>
</tr>
<tr>
<td>Ireland</td>
<td>16.5</td>
<td>5</td>
<td>0.76</td>
</tr>
<tr>
<td>France</td>
<td>20.1</td>
<td>15</td>
<td>0.73</td>
</tr>
<tr>
<td>Poland</td>
<td>30</td>
<td>0.63</td>
<td></td>
</tr>
</tbody>
</table>

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

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

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*Noone, O'Mahony, et al. Haemophilia 2020; Schlenkrich S et al, Haemostasologie*
Identifying what's important to patients
Consultation Process Outcomes: **Regulatory Process**

- **Revision of the current process to make it more applicable to rare and ultra-rare diseases.**
- **Leverage the centralized knowledge on top of the national one.**
- **Develop funding model beyond value-based decisions, for disease areas with small incentives.**
- **Develop creative endpoints to harmonize the regulatory and HTA approaches.**

"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.

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.

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.

“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

“This again relates to equity and what is fair”

HTA agency

“MCDA still not integrated”

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.
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 through 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

1. Performing a Targeted Literature Review on the existing understanding/use of EBA in Rare Diseases
2. Developing a Definition for EBA in Rare Diseases
   - Survey within key ISPOR SIGs
   - Focus Group Exercise with Rare Disease Experts
3. Manuscript describing the ISPOR Rare Disease SIG Definition, Importance, and Applications of EBA in Rare Diseases
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
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?

• 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
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References


