Do development, review and reimbursement frameworks need adapting to improve evidence generation and financially sustainable access for rare disease products?

4–5th October 2023

Oatlands Park Hotel,
Weybridge, Surrey, UK

WORKSHOP REPORT

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CIRS Centre for Innovation in Regulatory Science

Section 1: Executive Summary

Background to the workshop

It has been estimated that there are around 7,000 known rare diseases. The Global Genes Project suggests that approximately 300 million people across the world are affected by a rare disease.

The small patient populations with rare diseases raise practical and ethical challenges for randomised controlled trial (RCT) design. There can also be a need for companion diagnostics to go with new treatments to tackle rare diseases. Given these challenges, research and development (R&D) for rare diseases often needs to use alternative clinical trial and evidence-generation techniques, including the use of surrogate endpoints and indirect treatment comparisons. Acceptability of alternative approaches to clinical trials and evidence generation outside of clinical trials varies by regulatory and health technology assessment (HTA) agency. It has been argued that closer alignment is needed.

The development of treatments for rare diseases has been encouraged through regulatory incentives, introduced via legislation, including the US Orphan Drug Act and EU Regulation EC 141/2000. These provide the opportunity for new treatments in development to receive an orphan drug designation. Incentives can include fee relief, additional scientific advice support and in some cases, a period of exclusive marketing. A new EU HTA Regulation, coupled with draft EU Pharma legislation, includes a focus on treatments for rare diseases. However, not all countries have in place a formal orphan drug designation pathway.

There has been an increase in the number of new treatments given an orphan drug designation over time. Across the European Medicines Agency (EMA), Food and Drug Administration (FDA), the Pharmaceuticals and Medical Devices Agency (PMDA), Swissmedic and Therapeutic Goods Administration (TGA), 31% of new treatments were given orphan drug designation between 2011-2015. That compares to 38% between 2016-2020. CIRS data illustrates that in 2021, the proportion of approved new active substances (NAS) was high across these key regulatory agencies. Whilst this suggests that incentives for orphan drug development have resulted in new treatments for rare diseases being developed and licensed, this has also presented a challenge for HTA agencies and payers because there can be a high degree of uncertainty around the evidence for these treatments. Very few HTA agencies have specific pathways for assessing orphan drugs.

This workshop took a focused look at rare disease medicines, including their development, regulatory review, HTA and reimbursement, from the perspective of companies, regulators, HTA agencies, payers and patients.

Workshop objectives

1. Identify different stakeholder perspectives on the challenges and opportunities for adapting or improving regulatory or reimbursement frameworks for rare disease products.
2. Discuss how best to align evidence generation during development to meet the different needs of regulators, HTA and payers, enabling decision making at the time of review and reimbursement.
3. Make recommendations on how best to support evidence generation, particularly focused on regulatory, HTA and payer needs to address uncertainty at the time of decision, so as to enable greater patient access to rare disease products.

Venue

The workshop was held at the Oatlands Park Hotel, Weybridge, Surrey, UK, over two days: 4th and 5th October 2023.

Workshop Programme

Affiliations are stated as they were at the time of the meeting (4-5th October 2023).

Day 1: Wednesday 4th October 2023

SESSION 1: ADDRESSING UNMET NEEDS FOR IDENTIFICATION AND DEVELOPMENT OF RARE DISEASE PRODUCTS: HOW BEST TO ENABLE INNOVATION?	
09:00	**Chair's welcome and introduction** **Dr Brian O'Rourke,** Chair, CIRS HTA Steering Committee
09:10	**Rare disease product approvals: The changing regulatory and HTA landscape** *Background to the meeting – CIRS regulatory and HTA data on rare disease product approvals, change over time, approval time and international roll out.* **Dr Tina Wang**, Senior Manager, HTA Programme and Strategic Partnerships, CIRS
09:25	**Discussion**
09:30	**Development of rare disease medicines – which rare disease to target and what criteria do companies utilise to make the decision to develop new medicines?** *How are the diseases to develop for selected? What are the key criteria companies use? What role do incentives play? What are the high level challenges for companies?* **Company perspective - Martine Zimmermann,** Senior Vice President, Head of Regulatory and Quality R&D, Ipsen, France
09:45	**Discussion**
09:50 ***10:05*** ***10:20***	**Are incentives (current or planned) for the development, review and reimbursement for rare disease products fit for purpose from both a policy and practice perspective?** *What are the challenges? What works and what may need to evolve? How will the changes in legislation in the EU impact rare disease development and assessment?* **Patient viewpoint – François Houÿez,** Director of Treatment Information and Access, EURORDIS, France **Regulatory viewpoint – Dr Jayne Crowe,** CHMP Member, Health Products Regulatory Agency, Ireland **HTA viewpoint – Niklas Hedberg,** Chief Pharmacist, TLV, Sweden
10:35	**Discussion**
10:45	**Break**
SESSION 2: EVIDENCE GENERATION DURING DEVELOPMENT OF RARE DISEASE PRODUCTS- WHAT ARE THE CONSIDERATIONS TO IMPROVE OUTCOME PREDICTABILITY?	
11:15	**Engaging patients with rare diseases: How can the engagement upstream evolve to better support evidence generation and downstream decision making?** **Patient perspective - Alastair Kent,** Independent Patient Advocate, UK
11:30	**Discussion**

	Are today's tools for addressing small patient populations and clinical uncertainties during development of rare disease products sufficient to meet regulatory/HTA needs at the time of review/assessment or are new approaches required to bridge the regulatory/HTA gap? – *How to best understand evidence generation needs for rare disease products during development - is this the role of joint scientific advice?* – *What are the different types and levels of uncertainty that need to be considered?* – *Is it important to acknowledge these early in development?* – *How can HTA and regulatory stakeholders align on evidence needs from development?* – *How should this be balanced with post approval regulatory requirements - conditional or provisional approval?* **Panel discussion: 5-10 minutes viewpoint on the questions followed by a discussion with workshop participants**
11:35	**HTA viewpoint – Andrew Mitchell,** Honorary Professor, Department of Health Economics Wellbeing and Society, The Australian National University, Australia
11:45	**Regulatory viewpoint –Dr Anja Schiel**, Special Adviser, Lead Methodologist in Regulatory and Pharmacoeconomic Statistics, Norwegian Medicines Agency (*NoMA*)
11:55	**Company viewpoint – Mohit Jain,** VP, Value, Access and Strategic Pricing, Global Head BioMarin, UK
12:05	**Payer viewpoint – Dr Sahar Barjesteh van Waalwijk van Doorn-Khosrovani,** Member of the National Funder's Committee for Evaluation of Specialised Medicines and Companion Diagnostics, CZ; Affiliated with Leiden University Medical Centre, The Netherlands
12:15	**Discussion**
12:45	**Lunch**
SESSION 3: ADDRESSING REGULATORY AND HTA NEEDS AT TIME OF ASSESSMENT AND POST APPROVAL - WHAT STRATEGIES, METHODOLOGIES AND ACTIVITIES CAN BE USED?	
13:45	**Chair's introduction – Prof Hans-Georg Eichler**, Consulting Physician, Association of Austrian Social Insurance Institutions
	What are the practical considerations in utilising a life cycle approach to evolve the evidence and manage uncertainties for rare disease products? What needs to be place and is this practical? – *How to manage uncertainty and mitigate risks identified at the time of approval and reimbursement for rare disease products?* – *Use of post-licensing evidence generation - what are the opportunities and current barriers for rare disease products?* – *What role does real-world evidence and registries play?* – *What are best approaches?* – *Should there be a different approach for products which are approved first with a rare disease indication but the indications are subsequently widened?* **Company perspective – Dr Ramiro Gilardino,** Global HTA Policy Leader, MSD, Switzerland **HTA perspective – Dre Michele de Guise**, President and CEO, National Institute for Clinical Excellence in Health and Social Services (INESSS), Canada **Regulatory perspective – Dr Claus Bolte,** Chief Medical Officer, Swissmedic **Patient perspective – Dr Durhane Wong-Rieger**, President and CEO, Canadian Organization for Rare Disorders, Canada
	Discussion

	What role can multiple stakeholders play in the reimbursement framework for rare disease products to enable financially sustainable access? – *What should be the key considerations?* – *What role should performance-based managed entry schemes play in accepting the uncertainty associated with rare diseases?* – *Should knowledge generation be coupled to reimbursement?* – *Should the collection of data be mandatory if you receive reimbursement for orphan drugs?* **Panel discussion: 5-minute viewpoint on the questions followed by a discussion with the workshop participants** **HTA viewpoint – Dr Nick Crabb,** Interim Director, Science, Evidence and Analytics, National Institute for Health and Care Excellence (NICE), UK **HTA viewpoint – Dr Carlos Martin,** Advisory member General Directorate of the Common Portfolio of SNS and Pharmacy Service, Ministry of Health, Spain **Company viewpoint – Dr Ruth Pulikottil-Jacob,** Head, Global Health Economic & Value Access Rare Diseases, Sanofi, UK **Payer viewpoint – Dr Detlev Parow,** Former Head, Department of Medicines, Medical Remedies and Selective Contracts, DAK – Gesundheit, Germany
SESSION 4: SYNDICATE SESSIONS	
16:00	**Introduction to syndicate sessions**
16:05	**Break - Delegates to go to breakout rooms**
16:15	**Syndicate sessions begin. Topics for discussion:** **Topic A: Policy and practice perspective -** do current incentives need to evolve for the development, review and reimbursement of rare disease products? **Chair: Dr Sean Tunis**, Principal, Rubix Health, USA Rapporteur: **Stephane Callewaert,** Director - EMEA Policy Lead, Global Regulatory Policy & Intelligence, Janssen, Belgium **Topic B: Evidence development for regulators and health technology assessors** for rare disease products – how best to address (align and integrate) the needs of regulators and HTA? Chair: **Prof Adrian Towse,** Emeritus Director & Senior Research Fellow, Office of Health Economics, UK Rapporteur: **Dr Kate Betteridge**, Global Regulatory Portfolio Lead, Pfizer, UK **Topic C: Utilising a life cycle approach for rare disease products** to manage clinical uncertainties due to small patient populations - What are the considerations for HTA, regulators and payers? Chair: **Sharon Gorman,** Director, Regulatory Intelligence and Analysis, Pfizer, UK Rapporteur: **Lucia D'Apote,** Executive Director, GRR&D Policy, Amgen, Switzerland
18:00	**End of day one**
19:00	**Reception and dinner**

DAY 2: Thursday 5th October 2023

SESSION 4: SYNDICATE SESSIONS CONTINUE	
08:30	**Syndicate sessions resume**
10:15	**Break**
SESSION 5: SYNDICATE SESSIONS FEEDBACK	
11:00	**Chairman's introduction – Adjunct Prof John Skerritt,** University of Sydney, Australia
11:05	**Feedback of Syndicate discussions and participants' viewpoints**
12:00 **12:20**	**Real-world evidence for rare diseases – how should this evolve to meet the next generation of rare treatments?** **Regulatory perspective – Dr Junko Sato,** Associate Executive Director, Pharmaceuticals and Medical Devices Agency (PMDA), Japan **HTA perspective – Prof Wim Goettsch,** Professor HTA, Utrecht University and Special Advisor HTA, National Health Care Institute (ZIN), The Netherlands
12:40	**Discussion**
13.00	**Lunch**
SESSION 6: ADDRESSING UNMET NEEDS IN THE NEXT GENERATION OF RARE DISEASE: HOW BEST TO ENABLE INNOVATION, EVIDENCE GENERATION AND PATIENT ACCESS?	
14:00	**Chairman's introduction – Prof Steffen Thirstrup,** Chief Medical Officer, EMA
14:10	**Next generation of rare disease drug policy: ensuring innovation and patient access - what needs to be considered?** *Scientific advancements and regulatory policy initiatives have contributed to an increased number of approved rare disease treatments over recent years. As we move to the next generation of rare diseases, what are the key considerations to enable access within evolving health systems?* **Panel discussion: 5-7 minutes viewpoint on the questions followed by a discussion with the workshop participants** **Patient perspective – François Houÿez,** Director of Treatment Information and Access, EURORDIS, France **Regulatory perspective** – **Karen Reynolds**, Director General, Pharmaceutical Drugs Directorate, Health Canada **HTA perspective – Roy Foot,** Principal Pharmacist, Scottish Medicines Consortium **Company perspective – James Ryan,** Global Director, HTA Policy, AstraZeneca, UK **Academic perspective – Prof Lotte Steuten,** Deputy Chief Executive, Office of Health Economic (OHE), UK **Payer perspective - Dr Detlev Parow,** Former Head, Department of Medicines, Medical Remedies and Selective Contracts, DAK – Gesundheit, Germany
15:10	**Discussion**
15:30	**Chairman summary and close of meeting**

Key points from presentations

Please note, affiliations are stated as they were at the time of the meeting (4-5th October 2023).

Session 1: Addressing unmet needs for identification and development of rare disease products: How best to enable innovation?

Dr Tina Wang, *Senior Manager, HTA programme and Strategic Partnerships, CIRS, UK,* provided an overview of the orphan drug regulatory and HTA landscape in the last ten years. It has been recognised that there are many challenges to developing and bringing to market rare disease treatments. Many jurisdictions have an orphan drug designation within their regulatory frameworks, and there has been an increase in approvals of orphan drugs from 2013 to 2022 in Europe, the US, Japan, Switzerland and Australia. Many orphan drugs have used flexible regulatory approaches. However, there remain differences in criteria used for orphan designation leading to differences in how the same new active substances are classified by regulators. Variation in approaches to orphan drugs is evident across HTA agencies too. Many HTA agencies have flexibilities which are not specific to orphan drugs but can, and have been, used for them. The time HTA agencies take to assess orphan drugs is similar across many countries, however, there is variation in the timing of company submissions. Flexible approaches to access and in some countries, special funding mechanisms, can enable reimbursement.

Martine Zimmermann, *Senior Vice President, Head of Regulatory and Quality R&D, Ipsen, France,* provided a company perspective on how companies decide where to focus their research and development (R&D) efforts. Companies have responded to incentives to develop rare disease treatments yet face challenges with different models for reimbursement at the country level. There are multiple drivers of company investment decisions that include science, commercial potential, and unmet needs. Successful R&D requires multi-stakeholder collaboration.

François Houÿez, *Director of Treatment Information and Access, EURORDIS, France,* provided a patient perspective on the success of current regulatory incentives to develop rare disease treatments. There is debate on their success overall; there are more orphan drugs with marketing authorisation resulting from EU regulatory incentives, yet some believe that many orphan drugs – although not all – would have been developed in the absence of these incentives. The impact of proposals to change EU regulatory incentives for rare disease treatments is difficult to predict and all aspects of incentives need to be considered, including the role of competition. Patient groups, like EURORDIS, are well-placed to collaborate with multiple stakeholders in all aspects of development and access to rare disease treatments.

Dr Jayne Crowe, *CHMP Member, Health Products Regulatory Agency, Ireland,* provided a regulatory perspective on developing orphan drugs and EU regulatory incentives. There are recognised challenges for companies to successfully develop treatments for rare diseases and EU regulatory incentives have been in place to help. Proposed changes to the EU regulatory incentives cover several domains and could see an increase in the number of years companies are given market exclusivity overall. Changes to EU regulatory incentives will interact with other EU regulations. The proposals also revisit the definition of unmet need. Stakeholders need to work together through a variety of mechanisms, including early scientific advice opportunities, to help companies generate evidence that is needed to support regulatory, HTA and payer decision making.

Niklas Hedberg, *Chief Pharmacist, TLV, Sweden*, provided an HTA perspective on incentives for rare disease treatments. Incentives are not currently balanced; there are orphan drug blockbusters and at the same time, neglected rare diseases. The need for special treatment for orphan drugs is debatable; the characteristics of some common diseases can be just as severe or life-threatening as some rare diseases. There is always interest in the speediness of HTA decision making yet available statistics are not always transparent and may not identify the causes of delays, including delays driven by companies. It would be useful for stakeholders to gain insights into company decision making and participation in HTA processes. The TLV has made several recommendations to change its approach to help speed up access to rare disease treatments, including paying more for ultra-orphan treatments and lowering prices for blockbusters. More comprehensive changes to the system are needed in the future.

Session 2: Evidence generation during development of rare disease products - What are the considerations to improve outcome predictability?

Alastair Kent, *Independent Patient Advocate, UK*, provided a perspective on involving patients across the full range of activities, from development to access. Patient involvement adds value to all stakeholders' activities. Patients and their carers can tell stakeholders what matters most to them. Patient participation in research is increased when that research fits into their lives, rather than asking them to fit into a company development programme. Patient representatives can help set the tone of discussions with key agencies and work within broader government programmes. Improving access is a priority for patients and they can take part in access decision making as an independent party but may need support to do so. Stakeholder collaboration, including patient representatives, is fundamental to addressing unmet needs.

Andrew Mitchell, *Honorary Professor, Department of Health Economics Wellbeing and Society, The Australian National University, Australia,* provided an HTA perspective on uncertainty in decision making. It is recognised by HTA agencies that the evidence for rare disease treatments will be limited, albeit the degree of uncertainty will differ according to the specific rare disease, with some being much rarer than others. HTA agencies already consider the potential for evidence generation that could address uncertainties at the time of the initial HTA decision. International research collaboration could improve natural history datasets, which could help to address a key driver of uncertainty in the evidence base to inform HTA. Evidence is only one factor that influences HTA decision making.

Dr Anja Schiel, *Special Adviser, Lead Methodologist in Regulatory and Pharmacoeconomic Statistics, Norwegian Medicines Agency (NoMA), Norway,* provided a regulatory perspective on uncertainty. There are multiple drivers of uncertainty, and acceptance of uncertainty differs by stakeholder. HTA agencies must consider the societal impact of their decisions; there are trade-offs inherent in making decisions about allocating limited healthcare budgets. Patients must be involved in decision making, including providing their perspective on fairness.

Mohit Jain, *VP, Value, Access and Strategic Pricing, Global Head BioMarin, UK,* provided a company viewpoint on evidence generation for rare disease treatments. Uncertainty is inevitable due to small patient numbers, and this needs to be recognised and managed. Companies have to navigate different evidence standards in use by regulators and HTA agencies and there are not yet established methods to evaluate real-world evidence (RWE) that is used as part of submissions. Greater predictability in acceptable evidence would aid companies, not only in generating that evidence but

also in making decisions about which treatments to continue to develop and commercialise. The EU HTA Regulation that will be in place from January 2025 could help increase alignment through joint scientific advice and early advice opportunities as well as provide greater predictability to companies on what evidence will be acceptable to agencies. EU regulatory incentives for rare disease treatments have been successful, however, access is a challenge.

Dr Sahar Barjesteh van Waalwijk van Doorn-Khosrovani, *Member of the National Funder's Committee for Evaluation of Specialised Medicines and Companion Diagnostics, CZ; Affiliated with Leiden University Medical Centre, The Netherlands*, brought in a payer perspective on managing uncertainty. Limited evidence for rare disease treatments poses a challenge for regulators and HTA agencies. The Netherlands has an infrastructure that allows access to promising drugs that lack enough evidence to get reimbursed. It is called the Drug Access Protocol and is combined with a personalised reimbursement scheme. To maintain a resilient and sustainable healthcare system, we need to address the uncertainties related to evidence and costs by creating a national, and perhaps regional, infrastructure for building evidence and to develop pragmatic payment models.

Session 3: Addressing regulatory and HTA needs at the time of assessment and post approval – What are the strategies, methodologies and activities that can be used?

Dr Ramiro Gilardino, *Global HTA Policy Leader, MSD, Switzerland,* provided a company perspective on a life cycle approach to HTA of rare disease treatments. The timing of HTA varies across countries but a new definition of HTA has explicitly brought the life cycle into consideration. Reassessment can change HTA recommendations, informed by new clinical trial data and/or RWE. Ongoing work by HTA International (HTAi) is exploring when the life cycle approach adds enough value to offset the additional resources the approach requires. Companies face the challenge of navigating different evidence standards being used by regulators and HTA agencies, but there are opportunities to work with partners including patients on post-licensing evidence generation.

Dr Michele de Guise, *President and CEO, National Institute for Clinical Excellence in Health and Social Services (INESSS), Canada*, provided an HTA perspective on a life cycle approach for the assessment of rare disease treatments. INESS does not use a specific approach for orphan drugs; instead, the approach is adjusted according to the disease. That means rare disease treatments can be accommodated within the proportionate approach used by INESSS. A life cycle approach resonates with the Responsible Innovation in Health focus that underpins INESSS work. That includes horizon scanning and using managed entry agreements. There is an openness to RWE, although it is not expected to replace RCTs when they are feasible.

Dr Claus Bolte, *Chief Medical Officer, Swissmedic, Switzerland,* provided a regulatory perspective on the regulation of rare disease treatments. There is global interest in rare diseases against a backdrop of tight budgets. There have been increasing numbers of orphan drugs approved but differences in opinions remain about appropriate endpoints. Approaches to evidence generation and regulation are changing and becoming more complex. Sandbox approaches can enable experimentation and early engagement can shape evidence generation. International collaboration is needed, building on efforts like the Access Consortium and Project Orbis.

Dr Durhane Wong-Rieger, *President and CEO, Canadian Organization for Rare Disorders, Canada*, provided a patient perspective on development and access to rare disease treatments. Drug discovery, clinical trials and regulatory review have adapted to the challenges of bringing innovative therapies to small patient populations, but unfortunately, access pathways have not. There are alternatives to the commercial model of access, as demonstrated by gene therapy Strimvelis for severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID), which is now produced by nonprofit Telethon Italy and charged at the cost of manufacture. More creativity is needed when considering how to bring more rare disease treatments to market and how to capture their value. Financing is the real issue, not affordability. The life cycle approach can help spread the cost of rare disease treatments.

Dr Nick Crabb, *Interim Director, Science, Evidence and Analytics, National Institute for Health and Care Excellence (NICE), UK,* provided an HTA perspective on reimbursement frameworks for rare disease treatments. NICE has a different approach to treatments for very rare diseases, the Highly Specialised Technologies (HST) programme, which is applied based on published criteria. Access to rare disease treatments is enabled by managed access approaches, including the Cancer Drugs Fund (CDF). The approach includes data collection, commercial arrangements and an agreed exit strategy, should a treatment not be recommended following a re-review by NICE. Outside of the HST programme, NICE has also replaced the end-of-life modifier with a severity modifier, to put more weight on treatments for people with severe diseases across all types of disease.

Dr Carlos Martin, *Advisory member General Directorate of the Common Portfolio of SNS and Pharmacy Service, Ministry of Health, Spain*, provided an HTA viewpoint on managing uncertainty associated with rare disease treatments. Stakeholder involvement is part of the new approach to HTA being used in Spain, which includes involvement at key points: early dialogue, assessment and decision making. Uncertainty is always present for rare disease treatments and needs proactive management. A new approach using dynamic pricing and outcome-based approaches is soon to be published. This will feature patient and clinician involvement, mandatory data collection and a more proactive approach to horizon scanning.

Dr Ruth Pulikottil-Jacob, *Head, Global Health Economic & Value Access Rare Diseases, Sanofi, UK,* provided a company perspective on evidence needs for rare disease treatment decision making. Stakeholders have a shared interest in evidence and there is a need for greater harmonisation and a life cycle approach. Sanofi advocates for patient involvement in decision making, along with specific approaches in regulation and HTA for rare disease treatments that can adapt to the disease and treatment context.

Dr Detlev Parow, *Former Head, Department of Medicines, Medical Remedies and Selective Contracts, DAK – Gesundheit, Germany,* provided a payer perspective on managing rare disease treatments. Payers in Germany have seen an increase in the proportion of medicines expenditure being spent on treatments for a decreasing proportion of patients. The need for managed entry has changed over time: availability of medicines in Germany was double the European average in 2018-2020. Past experimentation with managed entry failed because of changes made to financial risk pooling between insurers in Germany, which disincentivised companies from continuing payment-by-instalment contracts. However, there could be renewed interest in managed entry. Experience with mandatory evidence generation for orphan drugs is limited because of implementation challenges.

Session 4/5: Feedback from Syndicate discussions

Topic A: Policy and practice perspective - do current incentives need to evolve for the development, review and reimbursement of rare disease products?

Recommendations

An overarching goal should be to improve predictability for all stakeholders, enabled by:

- **Exploration of different incentive models for treatments for ultra-rare diseases**, potentially including HTA requirements for evidence-generation learning from the SMC and special funding.
- **Research on improving the predictability of regulatory approval**, learning from current tools in use including the impact of joint scientific advice and other approaches that enable early multistakeholder dialogue.
- **Research on improving the predictability of HTA approval**, identifying common evidence requirements by learning from past HTA decisions on orphan drugs and experimenting through sandbox approaches.
- **Learning from managed access** in orphan drugs.
- **Improving predictability of access for patients**, including how to involve patients, and ensuring that they are kept up to date.

Topic B: Evidence development for regulators and health technology assessors for rare disease products – how best to address (align and integrate) the needs of regulators and HTA?

Recommendations

- **Exploring the development of a "working with patients" code of conduct to shift mindsets.** There is a need to counter the perception of conflicts of interest which can limit the involvement of patient groups. There could be scope to learn from existing practices to governance and to educate stakeholders on these.
- **Exploring the development of a structured approach to pre-approval evidence generation to increase alignment.** Could a checklist be developed to cover fundamental issues in evidence generation?
- **Increasing pre-competitive early engagement to increase alignment.** Increasing capacity and awareness could increase uptake.
- **Examining the extent of post-licensing evidence generation to support decision making.** There could be research into how well current post-licensing evidence generation is working, in order to optimise this in the future so that it meets multiple stakeholders' needs.

- **Exploring the development of a structured approach to post-licensing evidence generation to increase alignment.** Could a checklist help to refine post-licensing evidence generation so that it meets multiple agencies' needs? It could also consider how this can support managed access agreements and dynamic pricing.
- **Exploring how to increase opportunities for early engagement by small and medium-sized enterprises (SMEs).** SMEs may face greater capacity constraints and may need more support.

Topic C: Utilising a life cycle approach for rare disease products to manage clinical uncertainties due to small patient populations - What are the considerations for HTA, regulators and payers?

Recommendations:

- **Bringing together best practices for rare disease registries.** Lessons can be learned from current approaches to rare disease registries.
- **Rare disease registries should be routinely considered during early engagement.** Registries are typically a key source of evidence so should be considered early by all stakeholders.
- **Explore the development of an integrated value framework.** The framework could include infrastructure and learning from clinical societies and existing rare disease research platforms. It could even use sandboxes to support experimentation.
- **Evolution is needed in early scientific advice.** Lessons can be learnt now that there is more experience with early scientific advice to optimise the opportunity.
- **Transparency is needed at the HTA agency and payer interface.** The needs of payers and HTA agencies can differ; greater transparency could help explore differences and scope for greater alignment in evidence needs. In addition, there should be more transparency about prioritisation in different healthcare systems, which involves policy makers as well as payers.
- **Exploring the development of methodological guidance for HTA for rare diseases.** The guidance could help to set out the distinct challenges for evidence generation for rare disease treatments and how these can be managed.
- **Increase resourcing of HTA agencies.** Resources can limit the HTA agency's ability to engage with stakeholders. Greater resourcing or a new HTA funding model would help.

Real-world evidence for rare diseases – how should this evolve to meet the next generation of rare treatments?

Dr Junko Sato, *Associate Executive Director, Pharmaceuticals and Medical Devices Agency (PMDA), Japan*, provided a regulatory perspective and overview of ongoing activity in Japan to support evidence generation for rare disease treatments. RWD is seen as a key enabler to the development of rare disease treatments and support is offered to registry holders, via guidance from the Ministry of Health, Labor and Welfare and advice from PMDA. A new collaborative project has started between registry holders and PMDA that is not exclusively for rare diseases but is seen as particularly relevant to them. Knowledge sharing is facilitated through visits. Further support may be available in future with proposals for a new centre within PMDA to focus on paediatric and orphan drugs. There is interest in international research collaboration, not just on registries but also on other sources of RWD, to enable harmonisation. Harmonisation is needed across regulators but also in clinical practice. PMDA already engages with patients and will continue to do so; this is especially important as evidence can be generated more efficiently through wearables and smartphones.

Prof Wim Goettsch, *Professor HTA, Utrecht University and Special Advisor HTA, National Health Care Institute (ZIN), The Netherlands*, provided an HTA perspective focusing on uncertainty – which is predicted to increase over time for future rare disease treatments – and a refreshed approach to managed entry agreements (MEAs). ZIN has an ongoing project to learn lessons from MEAs that use registries. Four case studies are ongoing, including one on Libmeldy (atidarsagene autotemcel) to treat metachromatic leukodystrophy (MLD). An international registry for MLD has been set up to support clinical research as well as HTA decision making. There was an exploration of using the evidence generated by the registry in pay-for-performance agreements. Lessons have already emerged from the wider project including the importance of defining standard data sets that all stakeholders can agree to. Challenges remain including collection of resource use data. Work remains to increase the quality and transparency of registries and to improve coordination of the collection of healthcare information, with more international collaboration needed.

Session 6: Addressing unmet needs in the next generation of rare disease: How best to enable innovation, evidence generation and patient access?

François Houÿez, *Director of Treatment Information and Access, EURORDIS, France,* provided a patient group perspective on how policy should evolve for next-generation rare disease treatments. There should be a focus on meeting the needs of those patients with a rare disease that has been neglected in R&D to date, particularly ultra-rare diseases. A change in the approach to R&D is needed, moving to a 'collaboration first, competition second' model. This could make use of a variety of existing tools including EMA-HTA parallel scientific advice and EU data infrastructures. Once a new candidate product has demonstrated safety and efficacy then a public call could support competition on price. Joint HTA reports and European procurement could support distribution, with European price negotiation allowing for different prices in each country.

Karen Reynolds, *Director General of, Pharmaceutical Drugs Directorate, Health Canada*, set out a regulatory perspective discussing how agencies like Health Canada operate within a wider health and political landscape. A rare disease strategy has been published by the Canadian government. Health Canada will play a role as the strategy is implemented, albeit using its existing tools of priority review and special access programmes rather than a specific approach for orphan drugs. Regulatory

innovation, including modernising clinical trial design, is a key focus for the agency as well as working collaboratively with agencies within Canada and beyond. Health Canada is also working with HTA agencies within Canada to engage early with companies and to integrate their respective evidence needs. It is important to recognise that not all challenges rest with regulators or HTA agencies; data protection is part of industrial policy, for example.

Roy Foot, *Principal Pharmacist, Scottish Medicines Consortium (SMC)*, *Scotland,* provided an HTA perspective and an overview of SMC's pathway for ultra-orphan treatments, which uses specific criteria. The focus of this approach to ultra-orphan drugs is to identify evidence needed to inform a re-review conducted after three years of access. It includes a Patient Access Scheme (PAS) process to negotiate a discounted price with the company. In addition, Patient and Clinician Engagement (PACE) provides an opportunity for patients to set out what matters to them, and the wider impact of the disease. The results from the reassessment of the first ultra-orphan drugs to go through the pathway are expected soon. In anticipation of increased uncertainty in the evidence base for future orphan drugs, SMC anticipates more flexibility will be needed and the importance of patient voice will increase. Innovative pricing models could be needed too.

James Ryan, *Global Director, HTA Policy, AstraZeneca, UK*, provided a company perspective on the development of the next generation of rare disease treatments. Greater predictability would be welcomed, as this would help companies to generate evidence that is seen as valuable by regulators, HTA agencies and payers. The impact of proposals to change EU regulatory incentives is uncertain, however, the industry is concerned that there could be fewer rare disease treatments developed as a result. Incentives need to be looked at in the round including science policy, regulatory policy and economic barriers and uncertainties in pricing and reimbursement. Early multi-stakeholder engagement is seen as a key enabler for the future development of rare disease treatments, particularly as a way to harmonise and potentially compromise on the evidence needed by agencies.

Prof Lotte Steuten, *Deputy Chief Executive, Office of Health Economics (OHE), UK*, contributed an academic perspective. Uncertainty surrounds the impact of next-generation rare diseases and their treatments on patients, healthcare systems and wider society. Changing current EU regulatory incentives is controversial: current proposals are seen by some as at odds with innovation. HTA will need to evolve in response to next-generation rare diseases and their treatments, and more tension between value-based pricing and affordability is anticipated. More work is needed to explore the role of MEAs, both in terms of current models but also the potential to apply different models that have yet to be applied to rare disease treatments. The key is to ensure that the payment model responds to the specific challenge of the rare disease treatment. The extent of competition between next-generation rare disease treatments is hard to predict too.

Dr Detlev Parow, *Former Head, Department of Medicines, Medical Remedies and Selective Contracts, DAK – Gesundheit*, *Germany,* provided a payer perspective on the next generation of rare disease drug policy. Political promises impact expectations and staying within a target for contributions to healthcare insurance in Germany poses a sustainability problem given the ever-rising spend on rare disease treatments. Current legislation automatically assumes added value for orphan drugs, but this does not reflect assessments carried out on orphan drugs that have a budget impact that allows them to be formally assessed. A proposal was made to shift the focus to pricing negotiations rather than assuming the added value of orphan drugs, along with new payment models. Dynamic pricing is an interesting proposal where prices could potentially go up, as well as down, according to the evidence. If there is a political desire to fund orphan drugs, it follows that there should be specific funding allocated to orphan drugs, akin to the CDF in England. Equality in access across Europe also implies EU procurement for orphan drugs.

Section 2: Presentations

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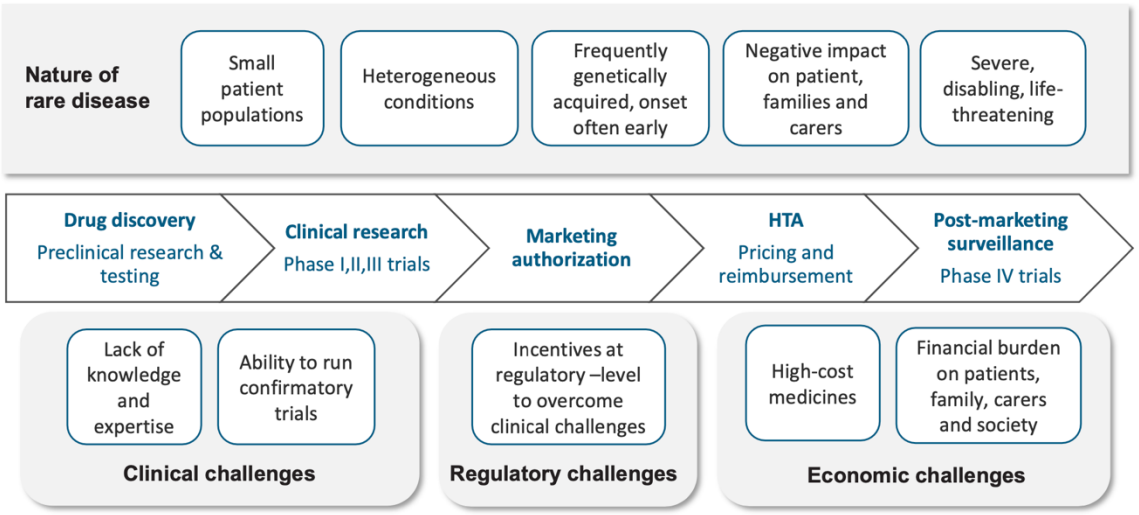
Session 1: Addressing unmet needs for identification and development of rare disease products: How best to enable innovation?

Rare disease product approvals: The changing regulatory and HTA landscape

Dr Tina Wang, Senior Manager, HTA Programme and Strategic Partnerships, CIRS

Challenges in developing treatments for rare diseases

There are several challenges for the development of rare disease treatments including clinical, regulatory and economic challenges (see below).

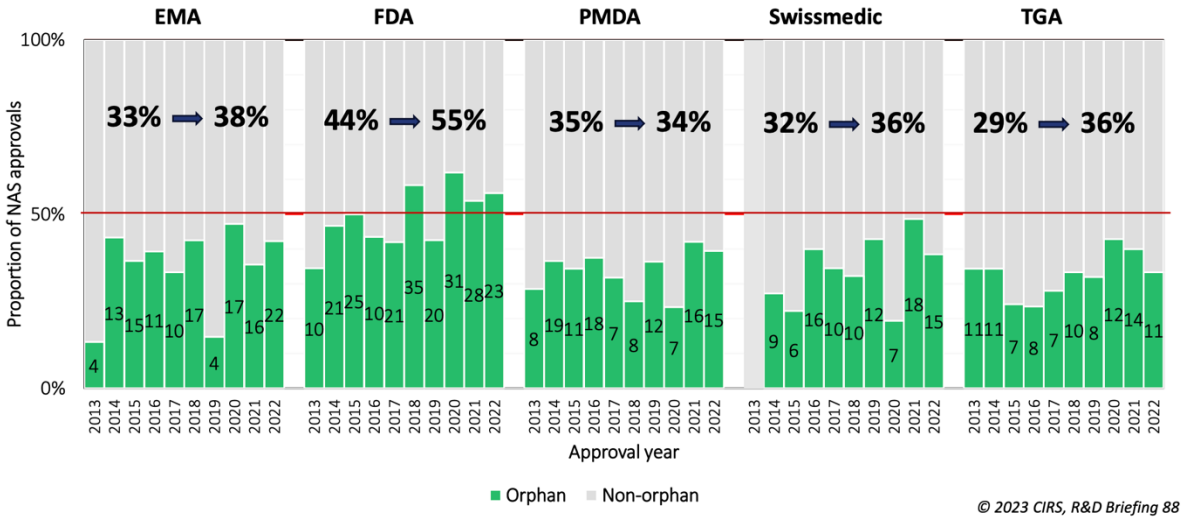


Adapted from :E. Nicod et al. / Health Policy 123 (2019) 140–151

Variation in regulatory classification of orphan drugs

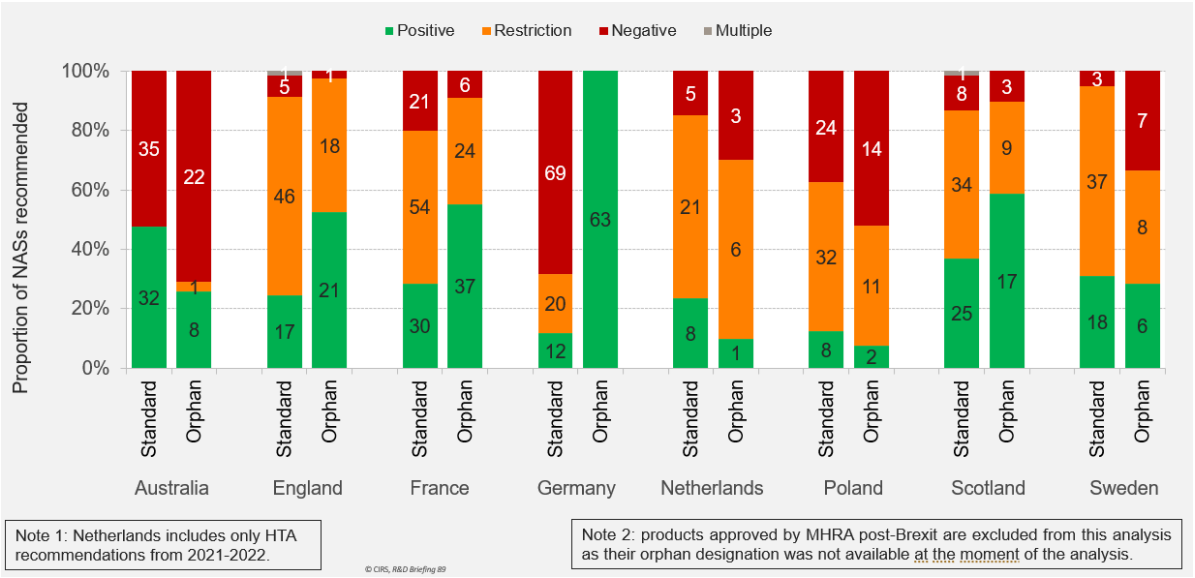
The terminology used to identify rare disease treatments varies across major regulatory agencies, with most, except for Health Canada, having an orphan drug designation. CIRS data shows that the number of new active substances (NAS) with an orphan designation given regulatory approval has increased over time across Europe, the US, Japan, Switzerland and Australia (see figure below). Orphan NAS approvals have been across several therapeutic areas, with about a third in cancer. Orphan drugs have generally been approved faster than non-orphan drugs (based on the median time to approval) and more than half of those approved have used at least one flexible regulatory pathway. Differences remain, however, in the criteria used for orphan drug designation, explaining why there are relatively few commonalities in the NASs given orphan drug designation across the reviewed regulators. In addition, there is a longer gap between the submission of orphan products

internationally compared to non-orphan products, which may be attributed to the smaller domestic companies that may be developing these types of orphan products; their strategies to roll out at a global level might be different to larger international companies.



Variation in HTA recommendations for orphan drugs

CIRS data shows variation in HTA recommendations for orphan drugs (see below). Germany is notable because its HTA approach presumes that the added benefit of a drug with orphan designation has been proven. However, there is a condition that annual sales of the drug must be below 50 million EUR, otherwise a benefit assessment will be carried out. Experience has shown that orphan drugs will not necessarily be found to have added benefit in Germany; in the past five years, four orphan products have been assessed because of their budget impact and their added benefit was not proven.



There is little variation in how long HTA of orphan drugs takes across HTA agencies. However, there is variation in the timing of company submissions to HTA agencies, which may be related to company launch strategies.

HTA agencies all have different approaches to assessing orphan drugs, be that through specific processes such as the Highly Specialised Technologies (HST) programme at England's National Institute for Health and Care Excellence (NICE), or more general recognition that there are exceptional cases where there is uncertain evidence (which can apply to both non-orphan and orphan treatments), as is the case in Canada. Only Scotland's HTA agency, the Scottish Medicines Consortium (SMC), has an orphan specific pathway, which is designed for assessing ultra-orphan drugs. Many orphan drugs have been given HTA approval using flexible access schemes and can also be funded from special funding mechanisms. One example is the English Cancer Drugs Fund (CDF). The CDF was not specifically designed for orphan drugs but has provided funding for many.

Conclusion

Regulatory

- Orphan approval proportion has generally increased over the past five years.
- About 1/3 of approved orphan products are anti-cancer or immunomodulators.
- Flexible regulatory pathways are used for orphan products, resulting in faster reviews.
- There is a longer gap between submission of orphan products internationally.
- Orphan designations differ between jurisdictions.

HTA

- HTA recommendations for orphan products differ in various regions, except for Germany.
- Submission strategy to HTA agencies resulted in divergence in overall roll out time.
- The Scottish SMC has a dedicated pathway for orphan products, while other regions can use alternative pathway or criteria.
- Different access route and funding mechanism can be used to enable access to orphan products

Development of rare disease medicines – which rare disease to target and what criteria do companies utilise to make the decision to develop new medicines?

Company viewpoint

Martine Zimmermann, Senior Vice President, Head of Regulatory and Quality R&D, Ipsen, France

Companies have increased focus on treatments for rare diseases

EMA data demonstrates increasing industry focus on developing treatments for rare diseases. Rare disease knowledge is dynamic; as companies undertake R&D, more knowledge about genetic mutations can emerge. This fuels investment as, with a known target, we can accelerate the development of potential treatments. There can also be very small patient numbers at the mutation level, which can provide a challenge to execute a development programme, or a number of programmes simultaneously if multiple companies choose to invest.

Orphan drugs can be treated differently for reimbursement

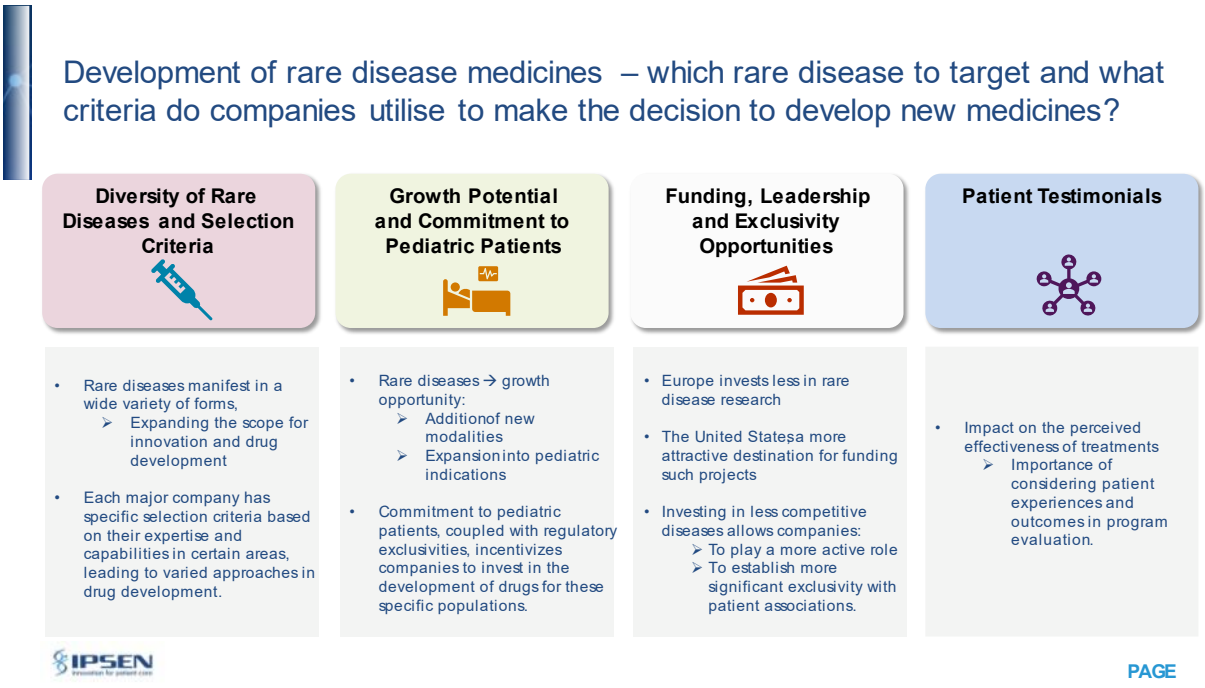
Company experience – and regulatory statistics – illustrate orphan designated treatments can be treated differently for reimbursement across geographies. Each country in the EU has its own criteria and mechanism for reimbursement. In France, orphan drugs have been awarded higher added therapeutic value more often than non-orphan drugs (Ref: GlobalData).

Drivers of R&D in rare disease treatments are multi-factorial

The reason companies invest in developing rare disease treatments is multi-factorial (see slide). Each major company has specific selection criteria based on the company's expertise and capabilities in certain areas, leading to varied approaches in drug development. When considering which rare disease to target, key criteria may include:

- High unmet medical need.
- Linkage of the biological target/pathway to the disease; possibility for disease modification.
- Concentrated centres of excellence and recognised key opinion leaders.
- Existence of natural history studies or patient registries.
- Existence of strong patient advocacy groups.
- Ability to identify the relevant patient population (genetic testing/clinical diagnosis).
- Clinically meaningful differentiation from the standard of care (as the standard of care often addresses symptoms rather than the root cause of the disease).

As well as the potential to respond to patients' unmet medical needs, the prospect of investment returns is needed to incentivise and drive continued R&D in rare diseases. We have seen companies respond to the current incentives to take bold risks that have changed the future for people living with rare diseases around the world through first and new treatments. Ipsen has focused on areas where no treatments exist, where there are more unknowns and hence greater risk. Although there are examples of regulatory flexibility in rare diseases, which are important, there is a need for greater regulatory flexibility to support continued investment.



Stakeholder collaboration is a must

Successful R&D, particularly in the rare disease space, requires collaboration between all parties: patients, regulators, clinicians, and centres of excellence working with industry. Collaborative approaches can help identify relevant endpoints to use in clinical trials, for example. Meaningful engagement requires resources.

Summary

Companies have responded to incentives to develop rare disease treatments yet face challenges with different models for reimbursement at the country level. There are multiple drivers of company investment decisions that include science, commercial potential and unmet needs. Successful R&D, particularly in the rare disease space, requires multi-stakeholder collaboration.

Are incentives (current or planned) for the development, review and reimbursement of rare disease products fit for purpose from both a policy and practice perspective?

Patient viewpoint

François Houÿez, Director of Treatment Information and Access, EURORDIS, France

Opinions differ on the success of current incentives

Although quantitative data exists – such as the number of orphan drugs given marketing authorisation – there are different opinions as to the success of incentives to develop rare disease treatments. Some view the number of orphan drugs given marketing authorisation as a success; others point to how few treatments there are against the backdrop of 7,000 rare diseases. Estimates suggest that just 4-6% of rare diseases have an authorised medicine. There has been a concentration of treatments for a small number of the same rare diseases.

Research is ongoing to explore the impact of different incentives to develop orphan drugs in the US versus Europe, including the impact of 10 years of market exclusivity in Europe versus 7 years in the US. The longer period in Europe could be discouraging diversification in R&D, leaving lower prevalence rare disease areas less well researched versus higher prevalence rare diseases. The US also offers tax credits for research. The approach to tax credits in the EU is not uniform, with Member States free to pursue their own policies; relatively few offer this incentive to companies.

European Commission research has suggested that incentives in Europe have only had a marginal impact on increasing the number of licensed rare disease treatments. Estimates suggest that 8 to 24 of 131 orphan medicines authorised in the EU since 2000 would not have been developed without incentives; the rest would have been developed anyway. They were, however, made available more quickly and reached more people across the EU, than before the Orphan Medicinal Products Regulation took effect. Despite this, access remains an area of dissatisfaction.

Proposals to change European incentives

The European Commission is proposing to reduce market exclusivity from 10 years to 9 years. Industry has raised concerns about the impact of the change on revenues. Could a solution be to accelerate uptake from the beginning? Work is needed across several domains to achieve this, from improving the quality of data going into HTA, greater engagement with HTA agencies and refining HTA methods.

The European Commission is also considering an additional year of market exclusivity when a new indication is licensed, instead of another 10 years. This aims to reduce the practice of ‘salami slicing’, where diseases are divided to create subgroups that can be considered rare diseases. To encourage companies to launch in all Member States, the European Commission is considering adding one year of market exclusivity.

The impact of proposed changes to EU incentives is unknown and difficult to predict. It may be that the most important incentives are not the regulatory ones.

Market dynamics interact with incentives

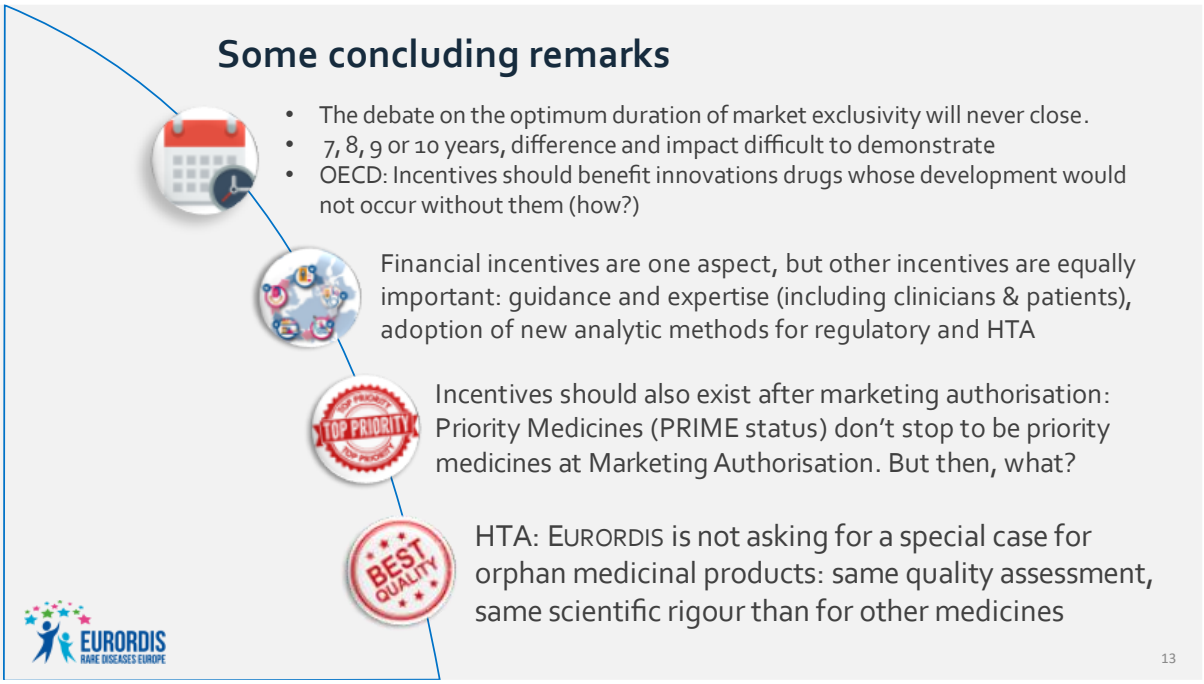
Less well understood are market dynamics for rare disease treatments. EURORDIS analysis from 2020 found that 40% of orphan drugs faced competition. Without effective competition, prices can remain high, in effect continuing the impact of market exclusivity incentives even after they have formally ended. Policy on incentives should consider competition so that incentives are viewed in the round.

Stakeholder collaboration is a must

Given the difficulties in attracting investment in rare disease R&D, stakeholders have to work together to reduce risks and timelines. Well-structured patient communities like EURORDIS, clear and transparent rules on national decision making for HTA, reimbursement and pricing, rapid implementation pathways as well as effective organisation of healthcare can help to attract investors.

Conclusions

The debate on the optimal duration of market exclusivity is unlikely to close. Financial incentives are one aspect, but other incentives are equally important, such as guidance and expertise by patients and clinicians, and the adoption of new analytic methods for regulatory and HTA that are more fit for purpose for rare diseases (but still maintain the same quality assessment and scientific rigour as for other medicines). Incentives should also exist after marketing authorisation to facilitate access to priority medicines.



Are incentives (current or planned) for the development, review and reimbursement of rare disease products fit for purpose from both a policy and practice perspective?

Regulatory viewpoint

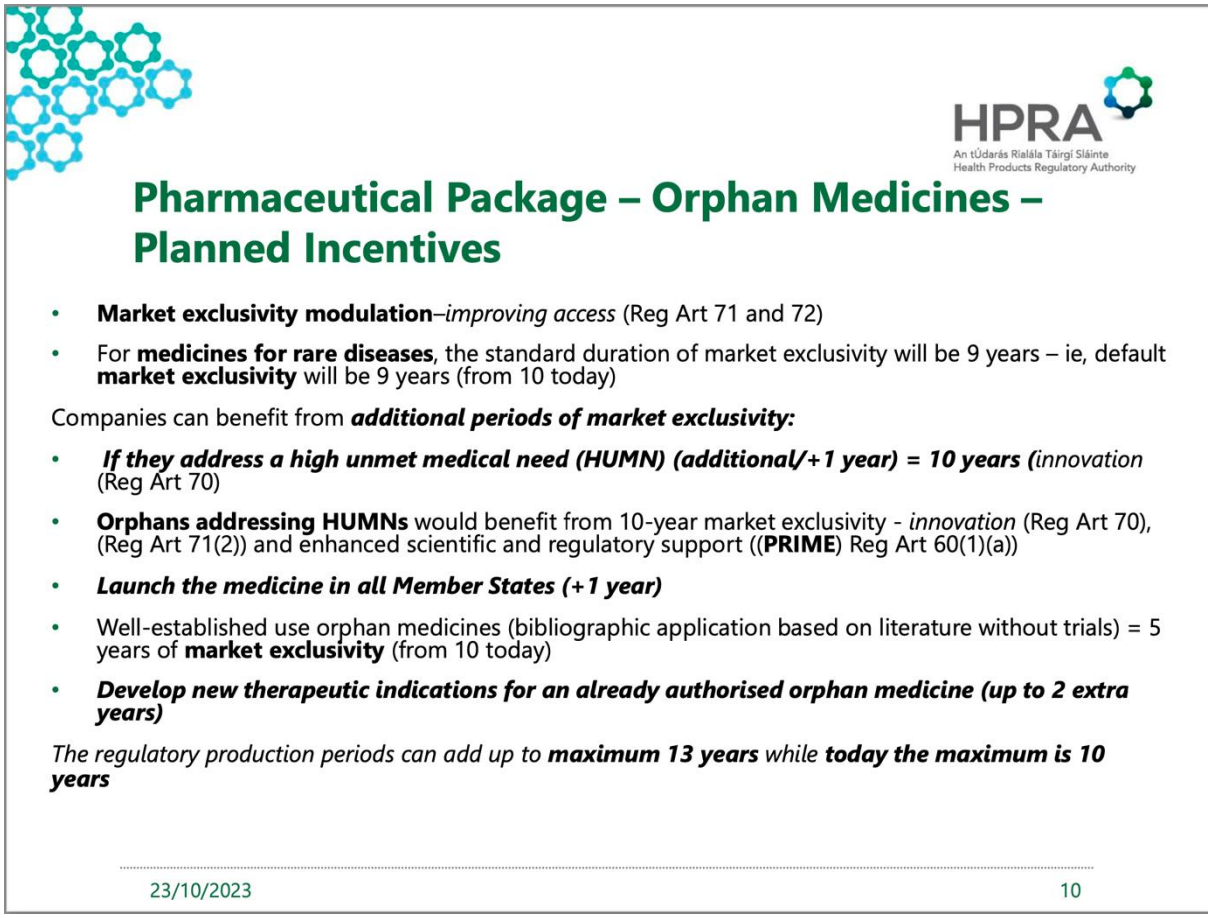
Dr Jayne Crowe, CHMP Member, Health Products Regulatory Agency, Ireland

Challenges in developing orphan medicines

There are many challenges in developing orphan medicines, including substantial costs, difficulties running clinical trials and ensuring requirements of HTA bodies, regulatory authorities and payers are met. Currently, there are several European regulatory incentives to help encourage the development of orphan medicines, such as EMA protocol assistance, market exclusivity, EMA/FDA parallel scientific advice and fee reductions in Member States.

Proposals to change European incentives

Proposals from the European Commission include strengthening EMA's role as well as process changes, for example, the Committee for Orphan Medicinal Products (COMP) will no longer be a stand-alone committee with responsibility for orphan designation. Changes to incentives could result in market exclusivity of a maximum of 13 years, instead of 10 years (see slide):



The definition of unmet medical needs is to be reviewed in the proposed legislation. There are also changes proposed regarding the regulation of paediatric medicines.

Conclusions

There are proposals for significant change in EU pharmaceutical legislation, including to incentives for orphan medicines. There is a need for a multi-stakeholder approach to the development of rare disease treatments, which can be further facilitated using existing tools like early scientific advice, as well as the proposed joint scientific consultations that will be implemented in January 2025 under the European HTA Regulation.

Are incentives (current or planned) for the development, review and reimbursement of rare disease products fit for purpose from both a policy and practice perspective?

HTA viewpoint

Niklas Hedberg, Chief Pharmacist, TLV, Sweden

Incentives need to be balanced out across rare diseases

Incentives for rare disease treatments are not in balance; there have been blockbuster drugs under the orphan drug label, which is not seen as reasonable from the payer and HTA perspective. At the same time, some rare diseases have seen little, or no R&D or treatments being brought forward. There remains debate about why there is special treatment for rarity *per se* as opposed to the severity of an illness and its prognosis, which could be comparable for someone with a more common condition.

Orphan drugs are not always treated differently for reimbursement

TLV has explored its decision making for rare disease treatments. There is no special consideration given to drugs with orphan designation; the characteristics of the disease and the treatment are considered, rather than the drug label. CIRS data have shown that the time from regulatory approval to HTA recommendation is longer for orphan drugs than for non-orphan drugs in Sweden. TLV works to the EU Transparency Directive requirement to take decisions within 180 days, hence delays are usually externally driven.

Interest in the speed of reimbursement and recommendations made about orphan drugs

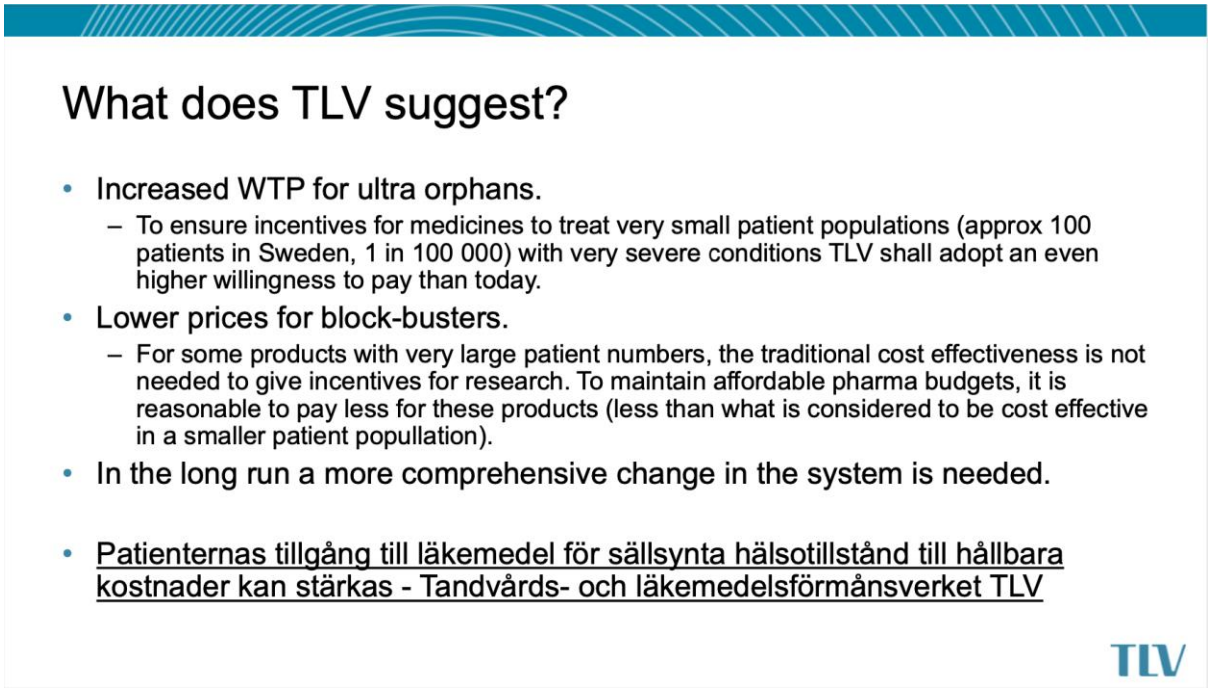
Any comparable statistics on the speed of TLV decision making and recommendations made to other countries, including within the Nordic region, generate debate. Transparency of the data underpinning some of these comparisons, as well as isolating the impact of the different incentives, are challenges.

Breakdowns at the country level for speed of HTA decision making and recommendations, for orphan and non-orphan drugs, are useful to stakeholders. These can be combined with surveys of companies to explore the issues more deeply. It would be useful to see more companies responding to such surveys to help stakeholders understand company decision making about whether and when to submit to HTA agencies.

Recommendations to change the approach to orphan drug reimbursement in Sweden

TLV was commissioned by the Swedish government to review its decisions for rare disease treatments and explore the factors, such as sales volumes and patient numbers, that can affect pricing decisions. The work also explored new payment models. TLV's work was limited to setting out budget-neutral recommendations. Its analysis found that around 60% of orphan treatments were made available to patients in Sweden, versus around 80% of non-orphan treatments.

TLV made recommendations for changes to their approach in September 2023 (see slide):



An English summary of the report is available from:

https://www.tlv.se/publikationer/publikationer/2023-10-02-starkt-tillgang-till-lakemedel-vid-sallsynta-halsotillstand---till-langsiktigt-hallbara-lakemedelskostnader.html

Summary of discussion from Session 1

Reforms need a clear goal

Policy needs clear goals to drive reforms. Sustainable access for patients – including patients beyond the EU - to effective treatments for rare diseases was articulated as the overarching goal. Tools by the Medicines Patent Pool can be explored to help achieve access for low and middle-income countries.

Incentives need to be considered in the round

Regulatory and even market access incentives are often focused upon regulatory and HTA approval, yet there is a need to consider incentives beyond these milestones ('hidden' incentives). Incentives can be both positive and negative. There is a high cost to companies to fund evidence generation, for example, registries that can be required by regulators for many years beyond marketing authorisation. Similarly, companies that incur costs of providing early access, through compassionate use programmes, hope for a shared commitment to access when regulators and HTA agencies assess those treatments. Competition also sets in play incentives for companies operating in the marketplace.

Reforms can fail

Reforms, such as capping prices on blockbuster treatments, have not always been successful. Industry can respond by withdrawing from negotiations or delaying the launch of products. Reforms can have international ripples too because of international reference pricings.

Session 2: Evidence generation during development of rare disease products - What are the considerations to improve outcome predictability?

Engaging patients with rare diseases: How can the engagement upstream evolve to better support evidence generation and downstream decision making?

Patient viewpoint

Alastair Kent, Independent Patient Advocate, UK

Patient involvement adds value for all stakeholders

There are five reasons patients should be engaged during R&D and beyond:

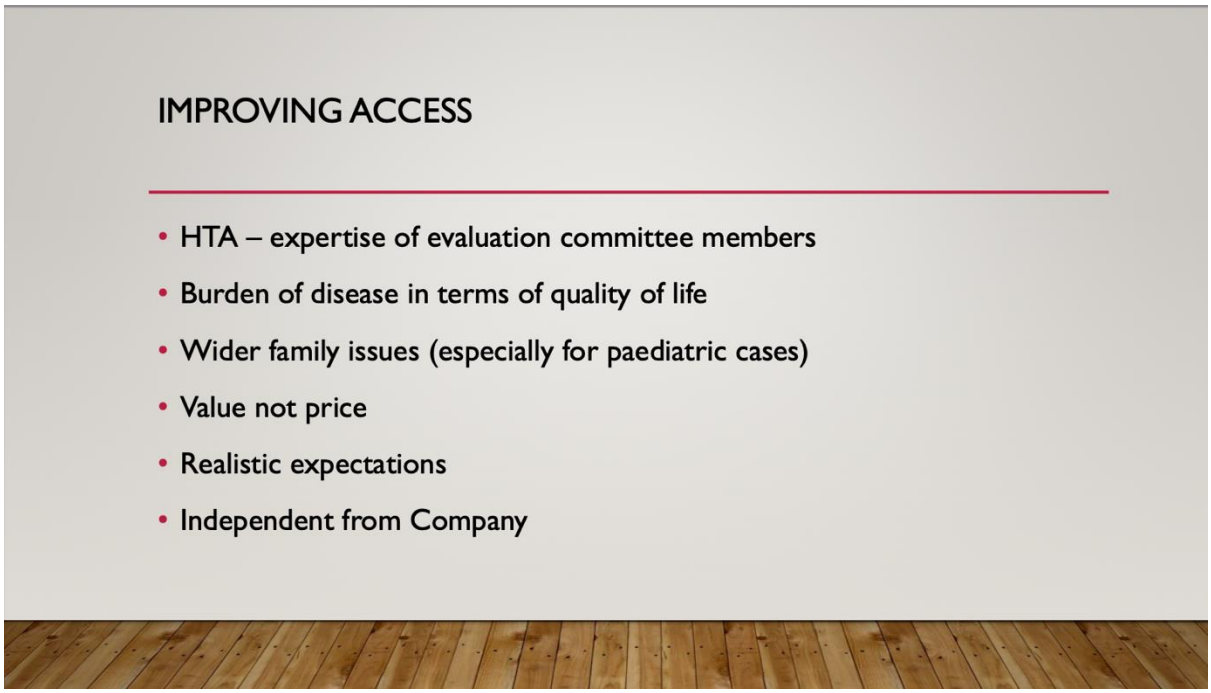
- To improve understanding of the rare condition
- To plan the R&D pathway to maximise efficiency and effectiveness
- To help recruit participants
- To help regulatory authorities understand the impact of the treatment
- To improve access.

Companies seek to address the things that matter most to patients and carers. Patients are willing to participate but they want R&D programmes to fit into their lives, rather than make their lives fit into a company R&D programme. For example, companies should explore remote collection of data. Consideration should be given to practicalities from the patient and their family's perspective. Companies should make use of patient support groups as they can enable the research via their networks of patients as well as clinicians with an interest in the rare disease space.

Patient representatives can set the tone of the discussions of committees within regulators, HTA agencies and others. Examples include the UK Rare Disease Stakeholder Forum, which brings together patients, the MHRA, NICE, the National Health Service (NHS), academics and the wider clinical community to help frame policy in the rare disease space.

Access is what matters most to patients

The best intervention in the world is useless if it stays on the pharmacy shelf and does not reach the patient. Access is key, but several improvements are needed to the HTA process and wider healthcare system (see slide). Patient representatives must be independent from companies but may also need support to help them provide evidence that is useful to those making decisions on access.



Summary

Patient involvement adds value to all stakeholders' activities. Patient participation in research is increased when that research fits into their lives, rather than asking them to fit into a company development programme. Improving access is a priority for patients and they can take part in access decision making as an independent party but may need support to do so. Stakeholder collaboration, including patient representatives, is fundamental to addressing unmet needs.

Rare disease products - are today's tools for addressing small patient populations and clinical uncertainties during development sufficient to meet regulatory and HTA needs at the time of review/assessment or are new approaches required to bridge the regulatory/HTA gap?

HTA viewpoint

Andrew Mitchell, Honorary Professor, Department of Health Economics Wellbeing and Society, The Australian National University, Australia

Evidence is inevitably limited for rare disease treatments

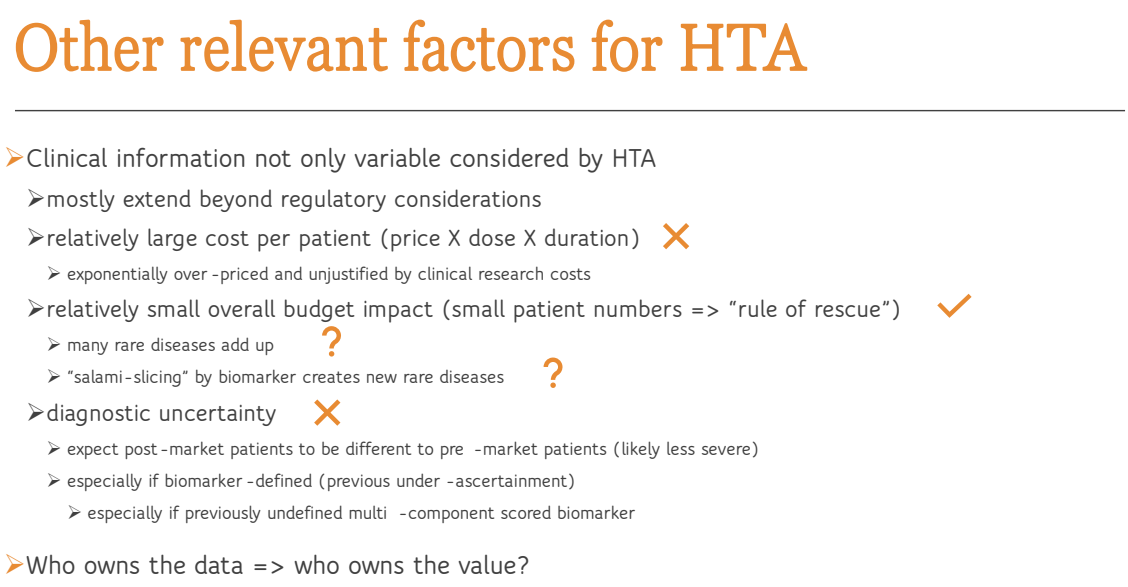
Not all rare diseases are equal; some are truly rare, and others are salami-sliced, with an example being salami-slicing by age where paediatric indications can be rare within a common disease. Given the nature of rare diseases, the evidence that will come to both regulators and HTA agencies will often be non-comparative, small sample, short-term studies with the earliest available clinical measure that is meaningful. HTA agencies already consider how to generate more data through tools like managed entry schemes, assuming that they can be confident that more time will allow more meaningful data to be generated.

International research collaboration is needed

There is value in moving beyond country-specific post-marketing studies; instead, studies should be multi-country and in the public domain, with the protocol, analysis and results all published, whilst ensuring patient privacy. Longer-running studies with more outcomes would also add value. In addition, it is vital to have historical controls. Care is needed to consider the value of biomarkers, which vary in their biological plausibility.

Multiple factors drive HTA decision making

Clinical information is only one factor that influences HTA decision making. There are several other factors, such as diagnostic uncertainty and who owns the data/value, that are considered by HTA decision makers (see slide).



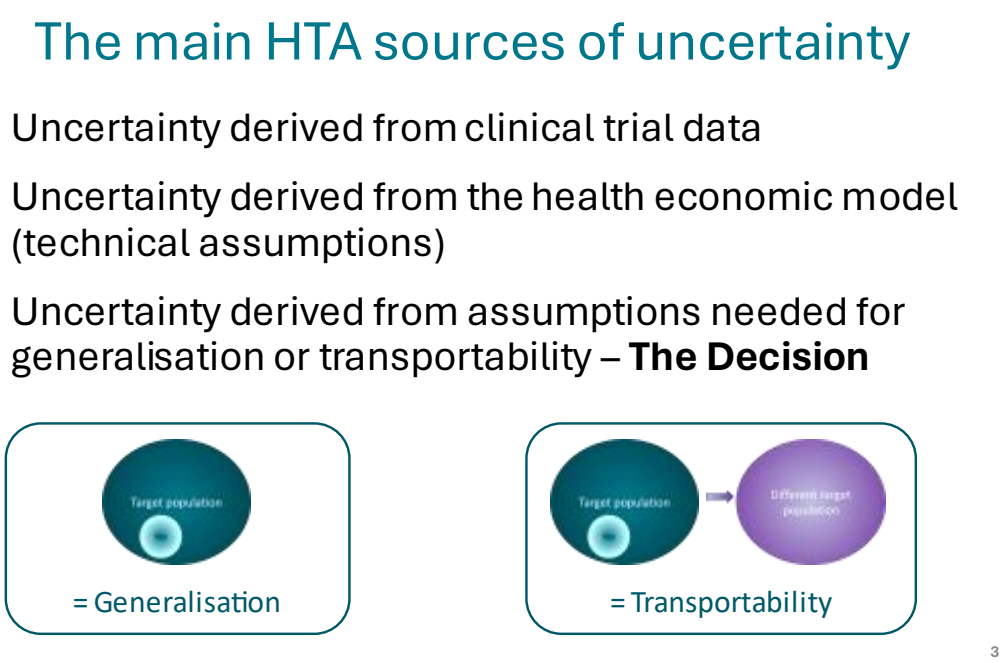
Rare disease products - are today's tools for addressing small patient populations and clinical uncertainties during development sufficient to meet regulatory and HTA needs at the time of review/assessment or are new approaches required to bridge the regulatory/HTA gap?

Regulatory viewpoint

Dr Anja Schiel, Special Adviser, Lead Methodologist in Regulatory and Pharmacoeconomic Statistics, Norwegian Medicines Agency (NoMA)

Multiple drivers of uncertainty

There are several sources of uncertainty in HTA: clinical trial data, the approach to the health economic modelling and the generalisability or transportability of the evidence. Uncertainty is, by definition, increased in rare diseases. As an example, it is difficult to disentangle the impact of many genetic mutations to be sure of the impact of a treatment.



Acceptance of uncertainty differs by stakeholder

The aim is to try to reduce uncertainty, to increase confidence in the treatment. Yet the decision uncertainty that regulators, HTA and patients are willing to accept differs. There are differences too between the participant in a trial and the patient who is to receive treatment.

Societal impact of decisions

While patients have a right to well-investigated, safe and effective drugs, it's not just for patients to decide whether a treatment should be paid for, because society plays a role too. Uncertainty is the real currency, with HTA helping to advise on the level of uncertainty surrounding a treatment and support those that need to judge if it is acceptable, or not. Just as for the budget, there is a limited amount of uncertainty that the healthcare system can accept. HTA agencies do bring in the patient perspective, but they must support decisions which affect all patients in the healthcare system. They have to consider "Do we spend on 5 or 10 patients in which we take up a budget that means we cannot treat 100 others?" Patients can help guide this, by providing their perspective to decision makers on whether this is fair or not.

Rare disease products - are today's tools for addressing small patient populations and clinical uncertainties during development sufficient to meet regulatory and HTA needs at the time of review/assessment or are new approaches required to bridge the regulatory/HTA gap?

Company viewpoint

Mohit Jain, VP, Value, Access and Strategic Pricing, Global Head BioMarin, UK

The solidarity principle underpins regulatory incentives for rare disease treatments

It is important to remember why orphan drug legislation was introduced. The purpose was to provide equitable access to treatments for those with rare conditions and to incentivise innovation. This principle of solidarity inevitably means that there is inherent uncertainty when developing treatments for rare diseases. Recognising this is the starting point to being able to manage that uncertainty. Overall orphan drug legislation has been successful in terms of regulatory approval of rare disease treatments, yet access remains a challenge.

Different regulatory and HTA standards for evidence

There are different evidence standards used by HTA agencies compared to regulators, in part driven by the different roles these agencies play. Regulators consider safety, quality and efficacy whereas HTA agencies influence access to budgets. HTA evidence standards can be very restrictive, not always considering the totality of evidence and sometimes not considering critical evidence. Whilst there is interest in RWE, there are not yet established methods for HTA agencies to evaluate RWE, nor how much uncertainty can be accepted within RWE.

Methods to assess evidence are being challenged. Industry and HTA agencies need to bring considerations of acceptance of uncertainty into their decision making, to help inform assessment of commercial viability and reimbursement. More predictability about what methods are acceptable and more alignment across agencies is needed for the industry.

EU HTA regulation could increase alignment

There is an opportunity through the EU HTA Regulation to increase alignment, helping companies manage their investment in drug development. Greater alignment could be enabled via joint scientific advice and early advice, helping to provide more certainty to companies about what evidence and methods are acceptable. This would be an input into the company's integrated evidence generation planning, to help them to produce evidence that meets all stakeholders' needs.

Variation in patient involvement in HTA

There is variation in terms of processes of patient involvement in HTA. In some jurisdictions, it is involvement in an agency meeting (though the amount of active participation can still vary), whereas in others it can take the form of a patient submission to the agency. Experimentation is happening though, for example, the Brazilian regulatory agency ANVISA has been using a social platform to bring in the patient perspective. This is critical because of the unique perspective that patients can bring about their rare disease. That can, in turn, help to reduce uncertainty.

Rare disease products - are today's tools for addressing small patient populations and clinical uncertainties during development sufficient to meet regulatory and HTA needs at the time of review/assessment or are new approaches required to bridge the regulatory/HTA gap?

Payer viewpoint

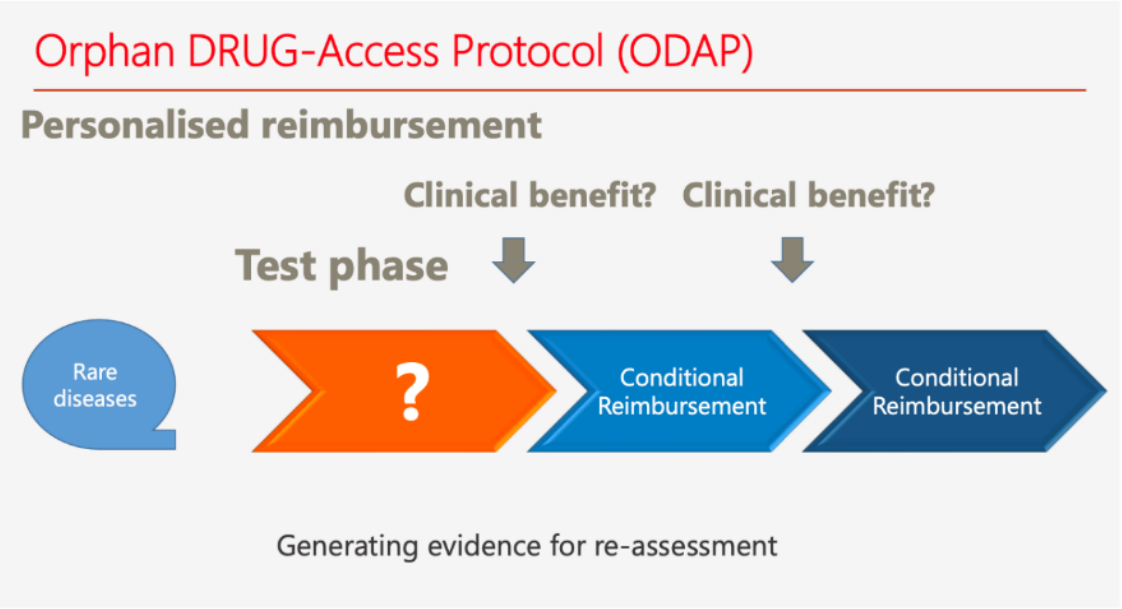
Dr Sahar Barjesteh van Waalwijk van Doorn-Khosrovani, Member of the National Funder's Committee for Evaluation of Specialised Medicines and Companion Diagnostics, CZ; Affiliated with Leiden University Medical Centre, The Netherlands

Limited evidence challenges regulatory and HTA agencies

There are similar challenges for regulators, HTA agencies and payers when it comes to decision making on orphan drugs; evidence issues such as single-arm trials, and surrogate endpoints, for example. Managed entry agreements can help, yet not all treatments are as promising as they first appear. There is an important role here for regulators to request post-approval studies.

Conditional reimbursement is an option in the Netherlands

In the Netherlands there is a formalised approach to conditional reimbursement in oncology: the Drug Access Protocol platform. This enables reimbursement from day 1 for the first 16 weeks for all patients but with the potential for this to be rebated by the company. A similar approach is available for orphan drugs, the Orphan Drug Access Protocol (ODAP) (see below). In ODAP the cost of treatments during the test phase is covered by the company, followed by conditional reimbursement.



Ongoing adaptive trial for repurposed treatments

There is an ongoing effort to help develop the evidence for repurposed treatments for rare mutations in cancer through an adaptive trial called the Drug Rediscovery Protocol (DRUP). Several other DRUP-like trials are currently commencing in different countries to facilitate access to precision medicine and collaboratively generate evidence within the Precision Cancer Medicine Repurposing System Using Pragmatic Clinical Trials (PRIME-ROSE) project. Ideally, in the final confirmatory stage of the DRUP trial, there should be a seamless transition from the experimental phase to regular care with the national HTA body's approval. In a pilot in the Netherlands, companies provide trial medication for the first 16 weeks and then the commercial medication is reimbursed, when there is evidence of clinical benefit.

Summary

To maintain resilience and sustainability in our healthcare systems and to keep pace with developments in rare diseases, we need to address uncertainties related to evidence and costs. This requires the development of infrastructure (national or perhaps regional) to generate evidence for very rare conditions, not only for authorised indications but also for off-label uses too. This should be coupled with pragmatic payment models, since together these can enable access for patients.

Summary of discussion from Session 2

Transitioning to a life cycle approach

The amount of uncertainty surrounding a rare disease treatment changes over time, hence the need to move away from a point-in-time decision to a life cycle approach. This shift is ongoing and supports a managed entry approach with evidence-building over time, including RWE. Such an approach needs to consider methods that can explore the cost of the wrong decision and the cost of gathering more and better evidence. Many HTA agencies start from a position of wanting to find a way to recommend a rare disease treatment and will be exploring whether they have sufficient confidence, based on the evidence available at the time, to be able to recommend a treatment. Evidence is one, but not the only, factor that drives HTA decision making.

Patients aware of trade-offs

Patients want to be involved in decision-making processes and recognise that there are budget constraints. Many will accept decisions that limit or prevent access where these decisions have been arrived at through a robust and fair process, including the option for appeal. Over time, patient organisations have evolved from disease-focused to national umbrella groups and those working internationally. That means that there are patient partners for multi-stakeholder work, at every level.

Openness to multi-stakeholder work

Agencies are typically open to working with companies and others on the evidence, including developing RWE methods. A proportionate approach is needed to explore what evidence is needed, not just wanted, to support decision making.

Improvements needed to natural history data

Natural history data is needed by all stakeholders, and this is an area that needs further work to improve the available evidence base. This data will often inform the comparator and can be an important driver of uncertainty. There is interest in cross-country sharing of knowledge. Data Analysis and Real World Interrogation Network (DARWIN) EU is an example of such work.

Curiosity about different pricing models

Value-based pricing is one pricing model, but there is also cost-plus pricing, which could have utility in situations where payers seek to pay below the cost of goods. Yet, cost-plus pricing could have the perverse incentive to reduce efficiency within companies as well as practical challenges for companies who have multiple products and diverse portfolios, making it challenging to confidently identify the costs of a specific treatment.

Session 3: Addressing regulatory and HTA needs at time of assessment and post approval – What are strategies, methodologies and activities that can be used?

What are the practical considerations in utilising a life cycle approach to evolve the evidence and manage uncertainties for rare disease products and what needs to be place and is this practical?

Company viewpoint

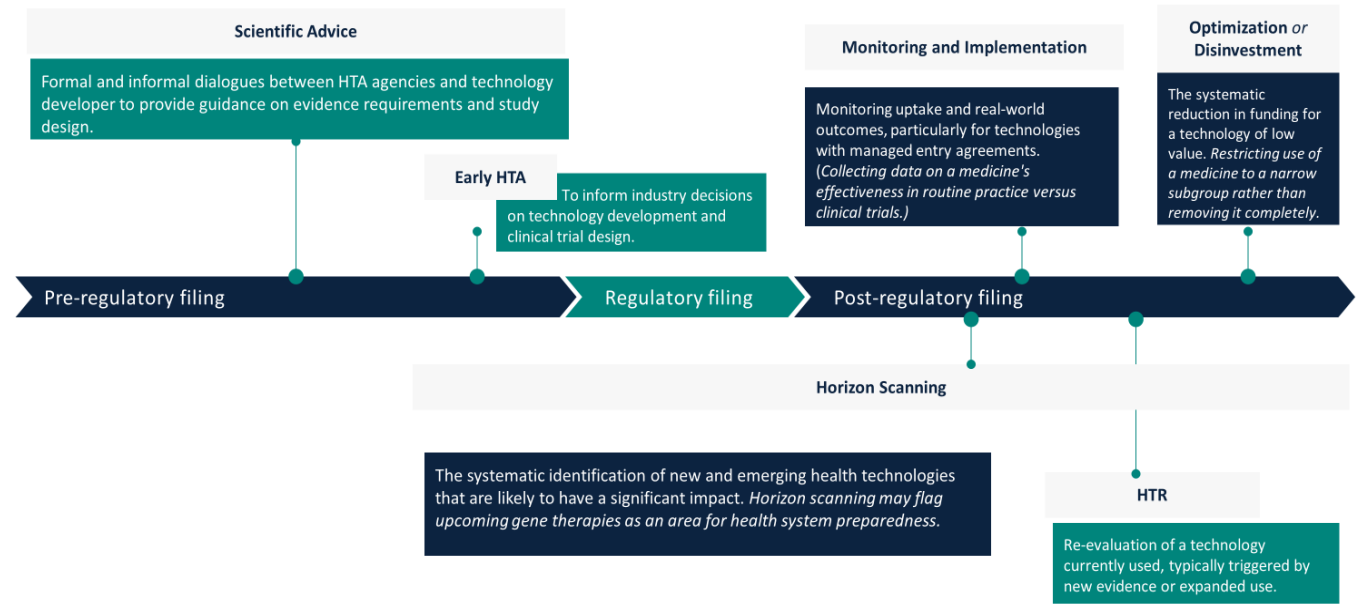
Dr Ramiro Gilardino, Global HTA Policy Leader, MSD, Switzerland

The timing of HTA varies

The practice of HTA agencies varies significantly in terms of the timing at which they conduct assessments throughout the life cycle of health technologies, be that early, or once a treatment has been established. A new definition of HTA has brought the life cycle of a technology into consideration. A life cycle approach to HTA encompasses various dimensions and factors, as shown in slide below.

Proprietary

What could be considered a life cycle approach in HTA?



Source: Adapted from . Trowman R, Migliore A, Ollendorf DA.. Int J Technol Assess Health Care. 2023 Feb 23;39(1):e15.

MSD 6

Where and why use a life cycle approach?

There is ongoing work to explore where and why a life cycle approach may apply to HTA. An HTAi multi-stakeholder task force has identified four different scenarios where a life cycle approach can add enough value to be worth the extra resources required. These are:

- Where technology may change over its life cycle
- Uncertainty relating to limited evidence at the time of HTA review
- Where a utilisation learning curve changes its outcomes
- Health service/delivery context impacts, or is changed, by the technology.

For example, in the case of uncertainty relating to limited evidence at the time of HTA review, horizon scanning and early scientific advice might be used while evidence to support a managed access scheme is being generated. As part of this process, the company generate the evidence and update the submission, which then goes into reassessment. However, there is not a one-size-fits-all solution for each scenario.

RWE supports the life cycle approach

RWE has a key role in supporting a life cycle approach. RWE can complement clinical trial data to ensure continued funding support for rare disease treatments and can also aid guideline development in areas with scarce RCT data, supporting informed decisions for patient outcomes.

HTA reassessment can change reimbursement decisions

In Germany, there have been HTA reassessments based on new clinical trial data, which has changed the initial recommendation for some treatments for non-small cell lung cancer assessed between 2019 and 2022.

Different regulatory and HTA agency evidence standards

A challenge to overcome is the mismatch between regulatory and HTA evidentiary requirements. Accelerated approvals do not align with the timeframes and decision making of HTA agencies, which can influence patient access.

Summary

To manage uncertainty and mitigate risks at the time of approval and reimbursement for rare disease treatments, companies must plan how to mitigate evidence gaps and have a clear access strategy, including the use of managed access schemes. In areas of high unmet need, RWE could sustain patient access through changes in reimbursement decisions or managed access. There are opportunities for the generation of evidence post-licensing, working with partners – including patients – to further understand the disease landscape and clinical pathways.

What are the practical considerations in utilising a life cycle approach to evolve the evidence and manage uncertainties for rare disease products and what needs to be place and is this practical?

HTA viewpoint

Dr Michele de Guise, President and CEO, National Institute for Clinical Excellence in Health and Social Services (INESSS), Canada

Orphan drugs are not always treated differently

At INESS, a global value appraisal approach was proposed in 2021, without a distinct approach for rare diseases, because the approach can be adjusted for assessing rare disease treatments. The principled approach is responsive to complexity; for example, when the treatment and decision are more complex, as can be the case for rare diseases, more stakeholders, including citizens, patients, clinicians and other experts, are invited to participate in the appraisal process.

Life cycle approach to HTA

INESS focuses on responsible innovation in health, which consists of a collaborative endeavour wherein stakeholders commit to clarify and meet a set of ethical, economic, social and environmental principles. This focus on responsibility and sustainability resonates with a life cycle approach to HTA.

A life cycle approach to HTA brings in new activities for agencies like INESS, including horizon scanning, managed entry agreements and even disinvestment, over time. INESS has used conditional reimbursement in the case of areas of high unmet health and social care needs, often with poor prognosis. Challenges have included insufficiently robust evidence, unstable economic modelling, difficulty determining a fair price and that decisions may engage health system resources over a long period of time.

Practicalities in using a life cycle approach

An RWE approach may not reduce the decisional uncertainties that matter most and so should not replace RCTs when they are feasible. The aim instead should be multicentre and/or pragmatic trials, funded through dedicated programmes, and greater sharing of clinical data and learnings from HTA. There is also a need to assess the performance of managed entry agreements to ensure that those that are administratively burdensome and ineffective are improved or withdrawn.

CONCLUSION

- "Responsible innovation means **taking care of the future** through collective stewardship of science and innovation in the present" (Stligoe et al., 2013)
- Value-based decisions in rare diseases require **clearly defined milestones** as well as **obligations** for all parties involved
  - Need to anticipate and mitigate both short- and long-term uncertainties
  - And to remain true to our respective missions
- While INESSS keeps evolving its methods and adapting to a complex context:

→ Issues surrounding reimbursement under difficult conditions must be made explicit, deliberated, and aligned with societal priorities

→ INESSS will rely on this social consensus to formulate fair, reasonable and responsible recommendations

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Institut national d'excellence en santé et en services sociaux Québec

What are the practical considerations in utilising a life cycle approach to evolve the evidence and manage uncertainties for rare disease products and what needs to be place and is this practical?

Regulatory viewpoint

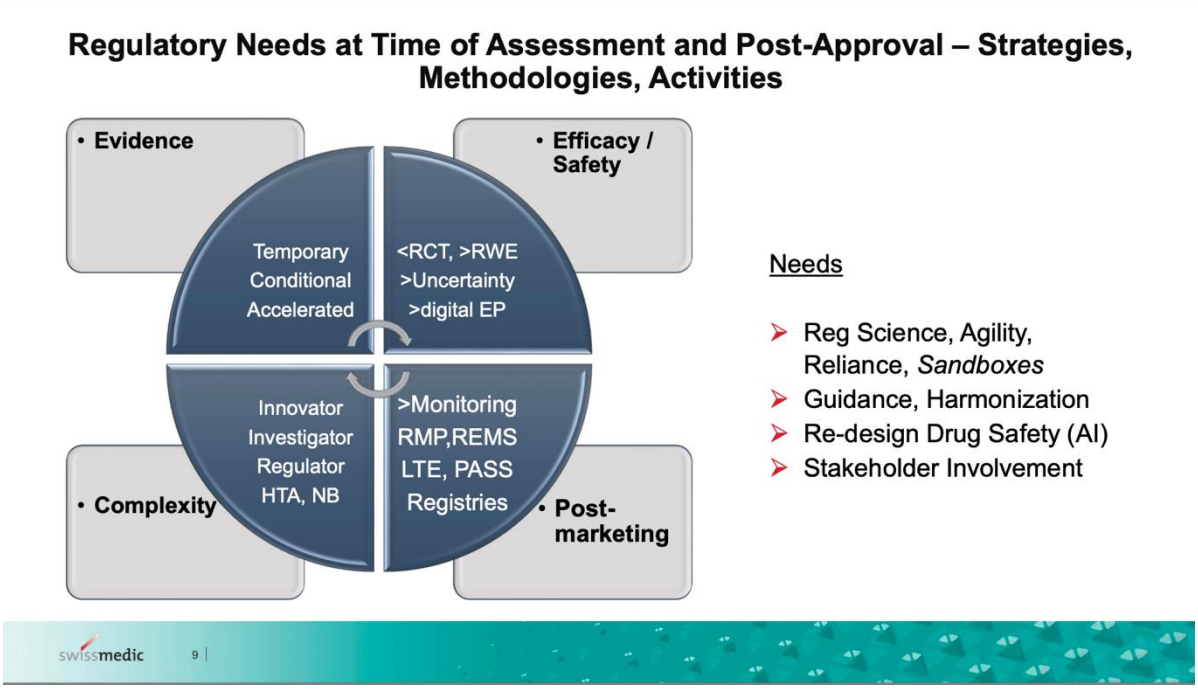
Dr Claus Bolte, Chief Medical Officer, Swissmedic

Global interest in rare diseases

The wider context is important; while there is more interest in rare diseases globally, this has been against the backdrop of tight budgets. There have been more orphan drug regulatory approvals in recent years, including conditional and accelerated approvals, particularly in oncology and haematology. Yet there are differences in opinions among regulators about the endpoints to use; for example, progression-free survival versus overall survival for genetically defined cancer subpopulations with an orphan drug designation.

Changing approaches to evidence generation and regulation

Changes are occurring that affect the evidence available at the time of regulatory assessment (see slide):



EP = End points, RMP = Risk Management Plans, REMS = Risk Evaluation Mitigation Strategies, LTE = Long Term Extension Studies, PASS = Post Approval Safety Studies

Experimental interventions, evidence generation and regulatory and HTA reviews have all become more complex with multiple stakeholders involved – innovators, investigators, patients, regulators, and HTA agencies, as well as Notified Bodies for combination products – with some activity taking place in parallel, but each taking up time. This affects the speed of access for patients. Joint advice (between regulators, HTA agencies, or involving both regulators and HTA agencies) is an approach to try to respond to this complexity.

International collaboration

There is also the option for joint regulatory review (i.e., simultaneous review via Project Orbis, or working sharing within the Access Consortium) and regulatory reliance. Experimental sandbox approaches might be useful in the early stages of development. Beyond traditional scientific advice, a more adaptive approach (bi-directional with the potential for adjustment regulatory requirements) and anticipatory models should be considered more frequently for novel product developments, in particular for cell- and gene-based therapies.

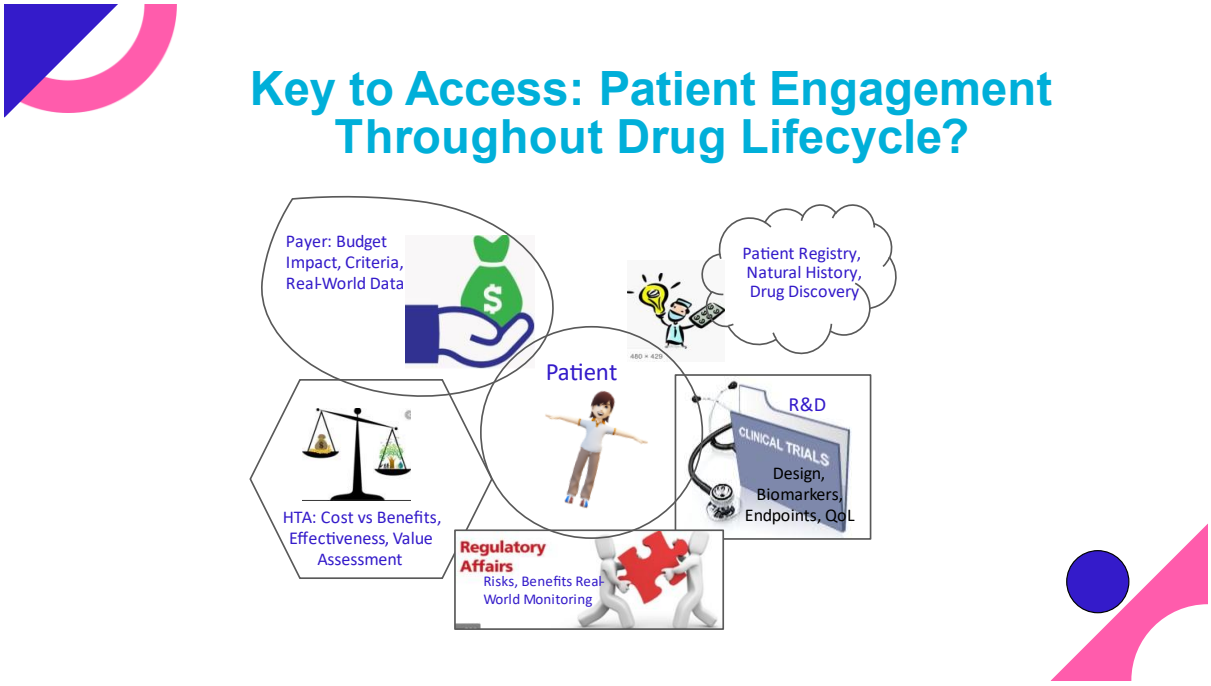
What are the practical considerations in utilising a life cycle approach to evolve the evidence and manage uncertainties for rare disease products and what needs to be place and is this practical?

Patient viewpoint

Dr Durhane Wong-Rieger, President and CEO, Canadian Organization for Rare Disorders, Canada

Access is the goal

Access is discussed at the population level, but the individual patient must also be considered. Patients want access to the right therapy in a timely and sustainable manner. This applies to middle and low-income countries as well as more developed ones. If there is no access for patients, then all efforts are for nought. Patient engagement throughout the drug life cycle may hold the key to access (see slide below).



Alternatives to the commercial model of access

Drug discovery, clinical trials and regulatory review have adapted to the challenges of bringing innovative therapies to small patient populations. Unfortunately, corresponding innovation on access pathways have not yet emerged, with the result that most patients do not get access to most of these therapies in a timely fashion, if at all. An early epitome that is still relevant is Glybera (alipogene tiparvovec) for familial lipoprotein lipase deficiency (LPLD). Glybera was the first gene therapy approved by the EMA in 2012 but with a $1 million price tag, which was considered exorbitant at the time, was withdrawn without a single vial being sold.

Fast forward to 2018, when gene therapy Strimvelis for severe combined immunodeficiency due to adenosine deaminase deficiency (ADA-SCID) was transferred from commercial partner GSK to nonprofit co-developer Telethon Italy because the very small number of patients rendered it not

commercially viable. About two dozen patients have been treated at an approximate cost of $660k but the treatment is only available in Milan and does not include other associated expenses.

Patients and their families are becoming more involved in the funding of research and development. For example, in Canada, the father of a child with Spastic paraplegia Type 50 raised the funds for his child and five others to be treated with an experimental gene therapy at the Hospital for Sick Children (SickKids), Toronto, for CAN $6 million.

Access can happen, even for high-cost treatments for very rare diseases, but there needs to be more creativity in terms of how to bring more of these drugs to market and how to capture their value. Can we start with patient access in mind and carefully examine how much data, evidence and cost effectiveness is really needed?

Question of finance, not affordability

There is a lot of hype about rare disease treatments destroying healthcare budgets, but this is not a reality. We need to shift the focus from affordability to financing. The life cycle approach can help to spread the cost of rare disease treatments.

Shared interest in RWE

RWE is important for the understanding of how well a treatment is working (or not). This knowledge is needed by all stakeholders including patients, who must make decisions on their treatment. However, RWE can unveil ambivalent results, unanticipated or rare negative outcomes, or that the value of benefit/risk does not support the price (which is usually high). Various countries in Europe are using RWE assessment as a condition of coverage to provide access to gene therapies and address decision uncertainties.

What role can multiple stakeholders play in the reimbursement framework for rare disease products to enable financially sustainable access?

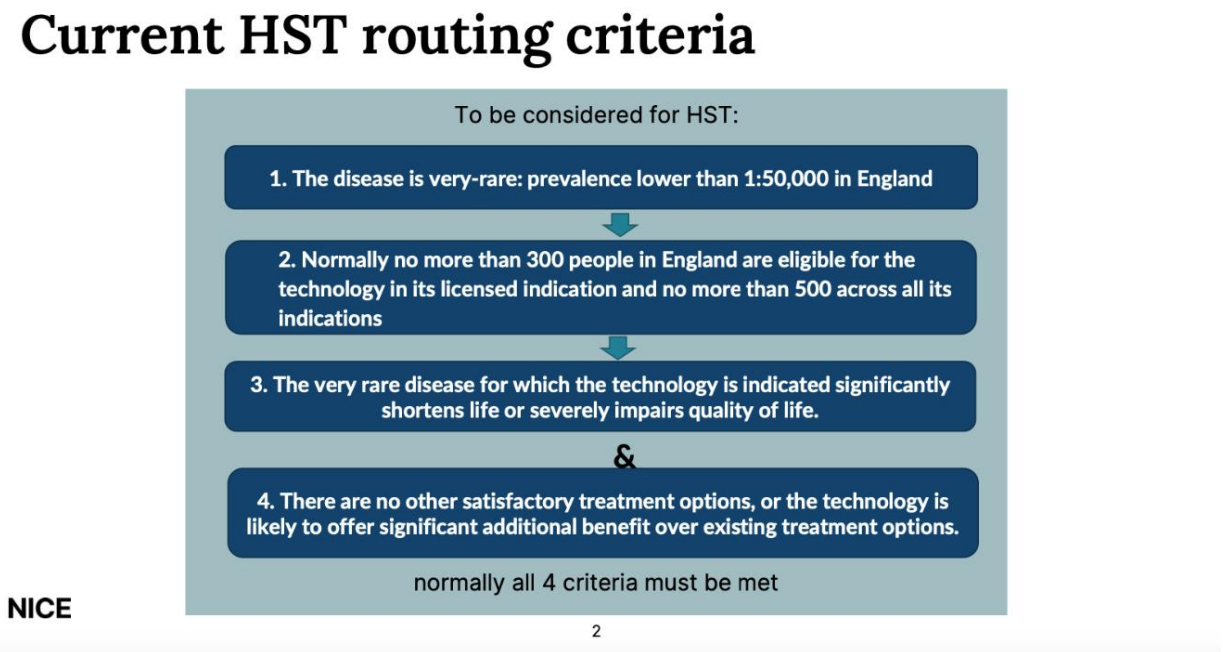
HTA viewpoint

Dr Nick Crabb, Interim Director, Science, Evidence and Analytics, National Institute for Health and Care Excellence (NICE), UK

Different approach to very rare diseases at NICE

The NICE Highly Specialised Technologies (HST) programme is particularly relevant for orphan drugs for very rare conditions. Between 2018-2022, around 31% of medicines designated as orphan drugs met HST eligibility criteria (shown below); the remaining orphan drugs were evaluated through NICE's standard Technology Appraisals (TA) programme. The HST programme has a higher willingness to pay than the TA programme, in recognition that an approach that maximises health gain at the population level may not be equitable for very small populations with ultra-rare diseases.

Based on the current pipeline, around 15% of orphan drugs meet HST eligibility criteria. There is still work to do to clarify the routing criteria for HST, to make them easier for stakeholders to interpret.



Managed access enables access

NICE has recommended the majority of orphan drugs it has evaluated – 98% during the period 2018 to 2022. Of these, 45% were recommended for use via managed access through the Cancer Drugs Fund (CDF). Managed access includes data collection, commercial arrangements, and an exit strategy, with a re-review by NICE. All three cases of managed access in the HST programme have been subsequently recommended and moved to routine commissioning.

New methods and processes

Wider changes at NICE were made through a review of its methods and processes, which was published in January 2022. A significant change was removing the end-of-life 'modifier' and replacing it with a severity modifier. This means that a rare disease treatment outside of HST can get a higher weighting for the quality-adjusted life years (QALYs) generated if it addresses a severe disease.

What role can multiple stakeholders play in the reimbursement framework for rare disease products to enable financially sustainable access?

HTA viewpoint

Dr Carlos Martin, Advisory member General Directorate of the Common Portfolio of SNS and Pharmacy Service, Ministry of Health, Spain

Stakeholder involvement

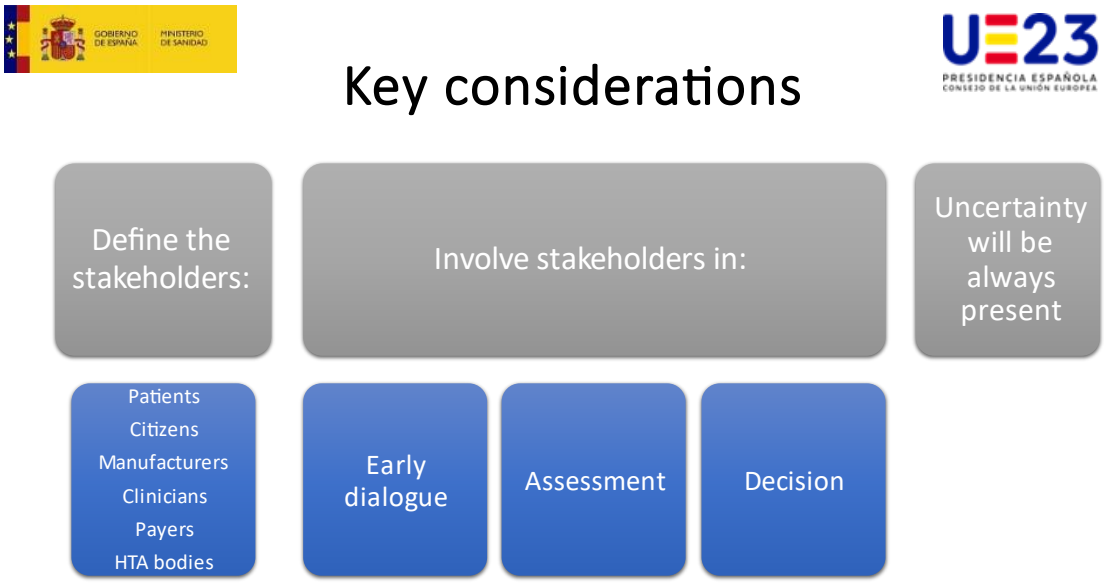
It is important to define stakeholders in the HTA process. Spain is changing its system: the new model includes patients, citizens, manufacturers, clinicians, payers and HTA bodies. Clinicians contribute via scientific societies. Involvement is at key points: early dialogue, assessment and the decision.

Uncertainty needs to be managed

Uncertainty is always present for rare disease treatments. Outcome-based managed entry agreements are necessary when a clinical uncertainty-based approach (dynamic pricing) cannot be implemented. It is crucial that outcome-based managed entry agreements involve patients and clinicians to define the best outcome for the rare disease.

Collection of data is mandatory

The collection of data is mandatory for outcome-based managed entry agreements. This helps to provide epidemiological data to support the development of new drugs. A more proactive approach should be taken to prospective data collection through the use of horizon scanning.



What role can multiple stakeholders play in the reimbursement framework for rare disease products to enable financially sustainable access?

Company viewpoint

Dr Ruth Pulikottil-Jacob, Head, Global Health Economic & Value Access Rare Diseases, Sanofi, UK

Shared interest in evidence

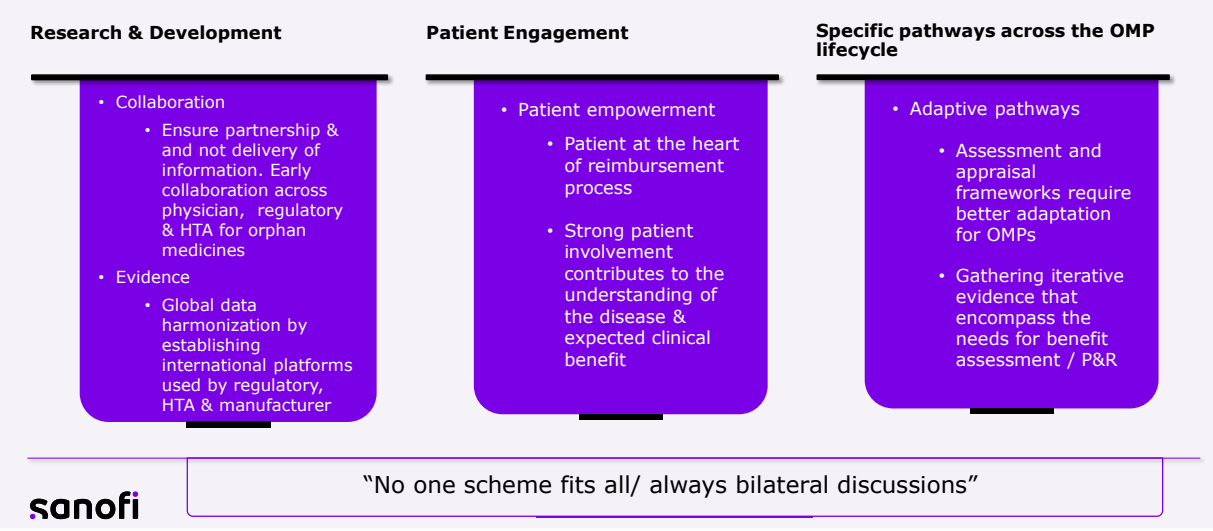
The only certainty is uncertainty when it comes to rare diseases. As the manufacturer, the role is to be a collaborator through the R&D process, a role that needs to start very early and involve working with multiple stakeholders. Evidence generation continues beyond R&D, yet in rare diseases it is fragmented. There is an opportunity for a more globalised and harmonised data platform that can be used by regulators, HTA bodies and payers as well as industry. There is a shared interest in understanding the life cycle of rare disease products.

Patient centredness

Sanofi advocates strongly for patient involvement in decision making, as they are the human face of evidence. Their input should go beyond understanding the disease symptoms, to acceptance of risk and the expected benefit of rare disease treatments.

Call for rare disease-specific approaches

As a company, we need to see adaptive pathways tailored for evaluating rare disease treatments. These adaptive pathways should provide an openness to utilise various evidence sources, employing an iterative approach to evidence generation. In instances where there is absence of data infrastructure or a lack of clear understanding of the disease, gathering iterative evidence plays a crucial role in obtaining approval for innovative drugs that address unmet needs. However, it is acknowledged that such adaptation may not be necessary for certain rare diseases where treatment pathways and real-world data already exist. Ultimately no one scheme fits all, hence the need for bilateral discussions and partnerships.



What role can multiple stakeholders play in the reimbursement framework for rare disease products to enable financially sustainable access?

Payer viewpoint

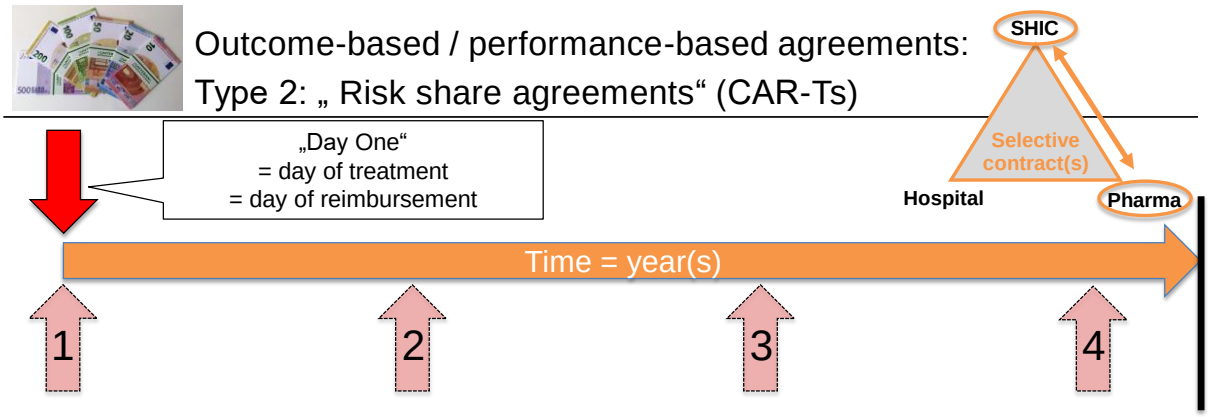
Dr Detlev Parow, Former Head, Department of Medicines, Medical Remedies and Selective Contracts, DAK – Gesundheit, Germany

Greater spending on fewer patients

Over time spending in Germany has moved from the Pareto principle – where 80% of costs were for 20% of patients in 2012, before most orphan drugs were approved – to spending more on even fewer patients. In 2020, Germany spent 80% of costs on 14% of patients. This is partly driven by disinvestment, which has generated criticism and there have been medicine shortages.

The need for managed entry changed over time

In Germany, the majority of orphan drugs are available – double the European average over 2018-2020 – with a median time to availability of 45 days. Given that all drugs become available in Germany as soon as they are authorised by the EMA, there is no need for managed entry agreements. However, there has been some experimentation with outcomes-based agreements in Germany for cell- and gene-based therapies in 2018 (see slide for example). These contracts were in addition to the usual reimbursement route for hospital drugs and were specifically between companies and statutory health insurers. Yet, for various reasons, such as changes to financial risk pooling between insurers, companies terminated the contracts. This was disappointing as it removed the ability to tackle the uncertainty of the durability of the treatment. However, there may be another renaissance of outcome-based contracts in future.



Possible conditions: hospitalisation, transfusions, factor VIII, non-survival, additional therapy needed

Measuring point: e.g 1 / 3 / 6 / n months

Rebate / refund

The longer it takes to meet the condition, the smaller the rebate / refund gets

No rebate / refund if condition not met during full period (e.g. one year)

Payer's benefit: Full reimbursement only, if treatment effective

7 Dr. Detlev Parow, DFGMA Jahrestagung, Berlin, 24.11.2022

Challenges to implement post-launch evidence generation

Knowledge generation by post-launch data collection is a very formal, bureaucratic and time-consuming procedure. In Germany, post-launch data is collected in specific circumstances: for pharmaceuticals with conditional marketing authorisation, exceptional marketing authorisation and orphan drugs. Data collection is currently ongoing for two orphan products: Zolgenmsa (onasemnogene abeparvovec) for spinal muscular atrophy (SMA) and Tecartus (brexucabtagene autoleucel) in mantle cell lymphoma. For seven other orphan products, post-launch data is still being discussed, or will not be collected because it is unfeasible.

There is a concern that for Zolgensma it will take 10 years for more data to be collected to support a re-assessment, and that this may conclude that further investigation is needed. There are also two other treatments for SMA, and it will likely emerge which treatment is better, even whilst the evidence generation requirements are in place for Zolgensma. The risk is that the health care system will have spent millions on Zolgensma even if it turns out to be an inferior treatment. A condition for reimbursement is that service providers must deliver data to a patient registry.

Summary of discussion from Session 3

The interplay between pricing and competition

It's recognised that registries will be providing evidence on the relative merits of three treatments in SMA, yet questions are being asked about whether all three should receive premium pricing given relative performance.

Managed entry agreements

There is a role for managed entry agreements (MEAs) especially when there is high uncertainty and high prices. Such agreements can play a role in exceptional circumstances. For sustainability, an agreed 'exit' is needed as part of MEAs, or perhaps even 'no pay for no performance'. The English Cancer Drugs Fund already operates with an agreed approach to exit as part of the commercial agreement reached. Implementation continues to be a challenge to MEAs and there is some frustration that despite being talked about, they are not more widely used.

Making the best use of available data

There are many calls for improved data infrastructure, including cross-country efforts, yet it comes at a cost and there are available data that are not always used. The European Reference Network for Rare Neurological Diseases was cited as an underutilised resource. Companies can also fund registries and the data may not be available to other stakeholders.

Feedback from Syndicate discussions

Topic A: Policy and practice perspective - do current incentives need to evolve for the development, review and reimbursement of rare disease products?

Chair: Dr Sean Tunis, Principal, Rubix Health, USA

Rapporteur: Stephane Callewaert, Director - EMEA Policy Lead, Global Regulatory Policy & Intelligence, Janssen, Belgium

Participants in Syndicate group A identified several incentives currently in use, which can be applied at different stages of the life cycle. The majority – except waivers of user fees – were seen as having the potential to evolve, albeit it can be difficult to achieve reform given that many operate at the country level, adding complexity (see table):

Current incentives	Type/Area of incentive	Fit for purpose or could evolve?	Comment
Tax incentive for clinical R&D	Development	Could evolve	Country-specific
Orphan Drug Designation	Review	Could evolve	Not lasting forever; may be withdrawn
User fees waived	Review	Fit for purpose	
Joint scientific advice	Review & Market Access	Could evolve	Not automatic currently; Should be foreseen early in process; Criteria for eligibility
Expedited regulatory pathways (Conditional/Accelerated approvals, PRIME)	Review	Could evolve	Do not translate into significant benefit for HTA
Transferable voucher	Review		Specific in certain regions (e.g. US)
Market exclusivity	Review & Economic	Could evolve	Subject to revision in new EU proposed legislation (more challenges) + country-specific
Incentives for reimbursement (Accelerated reimbursement funds)	Reimbursement	Could evolve	Country-specific; different in each country => complex

Notes: Review = Regulatory review

Participants were asked whether any additional or new incentives/approaches are needed and what potential policy changes or research might be needed to support these incentives. Key points captured from the discussion were as follows:

Terminology matters

The term 'incentives' is not always well received at the political level. A change in terminology could help to enable more reform. For example, incentives could be referred to as supportive measures to encourage R&D in diseases that affect small populations.

Incentive toolbox

The whole package of incentives is perceived as mattering more than individual incentives; a toolbox of incentives may be a useful way of thinking. There may be other incentive programmes and support to consider as part of this toolbox, for example, different countries' compassionate use programmes.

Life cycle approach to incentives

There is interest in developing a more predictable and holistic approach to incentives that would go through the whole life cycle of rare disease treatments. However, there may be difficulties implementing this, given that many incentives - particularly those related to HTA, reimbursement and pricing - are governed by different national legislations.

Learning from others

It is important to learn from countries that have models/approaches that are working well. Potential countries to look at are Taiwan, which has reimbursement incentives for certain diseases, and Japan with its Sakigake designation, a facilitated regulatory pathway that expedites the development of new drugs addressing high unmet needs.

Thinking beyond oncology

Incentives to bring to market rare disease treatments have worked in oncology, which may be due to the ability to 'salami slice' and receive incentives for each new indication. Further work is needed to understand why there has been success in oncology and how could this be translated to other disease areas.

Access in low- and middle-income countries

Access to rare disease treatments is challenging not only in high-income countries but especially in low and middle-income countries. There is interest in exploring how specific supportive mechanisms could be applied to improve access. The work of the Medicines Patent Pool was mentioned.

Knowledge sharing

The current landscape of incentives for rare disease treatments is complex, especially when considering HTA, pricing and reimbursement incentives at a national level. Mapping and producing a summary of current incentives could provide valuable insights to companies, especially small and medium-sized ones who may not have the same internal capabilities to monitor incentives as large

companies. CIRS mapping methods and the Mechanism of Coordinated Access to Orphan Medicines project could be useful for such an effort.

Recommendations

An overarching goal should be to improve predictability for all stakeholders. This can be supported through exploration of new models and bringing together learning from experiences with incentives used to date, including:

- **Exploration of different incentive models for treatments for ultra-rare diseases**. Different incentive models are needed to support the development, review and access to treatments for ultra-rare diseases. Although the challenge of small patient numbers is exacerbated for ultra-rare diseases, there are specific efforts to support building the evidence base; for example, Scotland has programmes in place for collecting data for the first treatment in ultra-rare therapy areas. Sharing data internationally could help, albeit there are challenges in comparing care across countries. Special funding and procurement systems could be explored too, be that at the country or regional level.
- **Research on improving the predictability of regulatory approval**. CIRS could analyse the impact of current approaches like joint scientific advice, accelerated access and PRIME, on the predictability of success for rare disease treatments. This research could also explore opportunities to foster multi-stakeholder dialogue at the early stage of development.
- **Research on improving the predictability of HTA approval.** All stakeholders could explore how to develop a consensus on the data that needs to be collected to support HTA decision making and coordination. CIRS could analyse how the assessment of data within HTA was conducted for orphan drugs. A sandbox approach could be used to explore approaches to share data collection and analysis across countries.
- **Learning from managed access in orphan drugs.** CIRS could analyse experience with contracts that have been used for orphan drugs.
- **Improving predictability of access for patients.** For patients, they must be kept up to date on access and information should be in their language. Industry and regulators could support such efforts, alongside others.

Topic B: Evidence development for regulators and health technology assessors for rare disease products – how best to address (align and integrate) the needs of regulators and HTA?

Chair: Prof Adrian Towse, Emeritus Director & Senior Research Fellow, Office of Health Economics, UK

Rapporteur: Dr Kate Betteridge, Global Regulatory Portfolio Lead, Pfizer, UK

Participants in Syndicate group B were asked to discuss different stakeholders' considerations for evidence generation, the challenges that need to be overcome to meet the needs of regulatory and HTA agencies and potential solutions to these challenges. Key points captured from the discussion were as follows:

Multi-stakeholder work is vital

In the context of small patient populations and uncertainty, multiple stakeholders must be brought together to consider pre- and post-marketing evidence generation. Often this will involve a registry, which can be developed pre-authorisation.

Think 'international'

Increasingly stakeholders need to adopt an international mindset. There needs to be early thinking about what data exists, and how to integrate data from different countries, as far as possible. There will be challenges, including missing data and the need to work through data-sharing agreements and data ownership.

Think 'patient'

Patients are key partners in evidence generation. Their input could shape the definition of what is the minimum clinically important difference. However, the neutrality of patients and their representative groups can be questioned when they work with industry, as this can be seen as a conflict of interest. As part of evidence generation discussions, including as part of early engagement opportunities, the burden of data collection on patients must be considered.

Common issues in pre-approval evidence generation

For many rare diseases, there will be shared challenges in generating the evidence. These include developing or accessing existing natural history datasets, trial design, choice of comparators, linking surrogate endpoints to clinically meaningful measures and dosing strategies. A checklist or protocol could be useful for guiding discussions and facilitating alignment on pre-approval evidence generation during early dialogue.

Pre-competitive early engagement opportunities can be limited by resources

There are opportunities for early engagement during the pre-competitive stage. Examples include the FDA Patient-focused drug development (PFDD) meetings. The Centre for Medical Technology Policy (CTMP)'s Green Park Collaborative was another option, but no longer exists, demonstrating the

challenge of sustainability for such efforts. Determining priority diseases to discuss through these opportunities, as well as resourcing such efforts, is challenging. Yet they offer the potential to increase alignment in the evidence that regulators, HTA agencies and payers would like to see to support their decision making, albeit there are limits to the degree of consensus that emerges from such engagement.

Competitive stage early engagement opportunities face capacity constraints

Several mechanisms offer the opportunity for dialogue with multiple stakeholders on evidence generation. They have advanced in recent years, however, capacity constraints limit access to those mechanisms, with parallel EMA/HTA body scientific advice having limited slots. Engaging at the national level can be time consuming for companies. Just as with pre-competitive early engagement, talking with both regulators and HTA agencies in parallel has the potential to increase alignment in evidence needs. However, some companies' experience is that consensus on key research questions or evidence requirements does not emerge.

Challenges in early engagement for small and medium-sized enterprises

Small and medium-sized enterprises (SMEs) may have more limited resources to support their early engagement with regulators and HTA agencies, yet they may also be the developers that would benefit the most from these opportunities. There are some discounts already for SMEs.

Post-license evidence generation opportunities and dynamic pricing

Continuing to generate evidence post-licensing is being done, but the extent of this is unclear. There may be further opportunities to refine evidence generation at this point to ensure it fits regulatory, HTA and payer needs and increase alignment. This may be being hampered by a lack of transparency in post-licensing evidence-generation activities. Could this post-licence evidence be used more often as part of managed access approaches too? It could be useful to explore real-life performance, durability of response, indirect comparisons and even support exit from managed access. Dynamic pricing could also be explored as part of this.

Transparency

There are concerns amongst some about a lack of transparency in the protocols that underpin evidence generation to meet the needs of regulators, HTA agencies and payers. This could be hindering the ability to identify commonalities and stifling alignment. Similarly, transparency in terms of study results is seen as a key principle.

Scenario planning

There is a need to identify potential scenarios as a rare treatment comes into the market such as new entrants to the market. This would allow for a plan for both evidence generation and managed access agreements to respond to such market dynamics.

Recommendations

- **Exploring the development of a "working with patients" code of conduct to shift mindsets**. Underpinning this should be the recognition of the very small number of patients, and patient representatives, who work on a specific rare disease. There are often very few who would not have had some engagement with industry and there can be a perception of a conflict of interest arising from this engagement. CIRS could support such work, building on existing practices and documents, for example, from the EMA Patients' and Consumers' Working Party, Innovative Medicines Initiative (IMI) PARADGIM project, Council for International Organisations of Medical Sciences (CIOMS) Working Group XI and EURORDIS. Education could help to shift mindsets too.
- **Exploring the development of a structured approach to pre-approval evidence generation to increase alignment.** CIRS could support the development of a checklist to cover fundamental issues in pre-approval evidence generation during the development of rare disease treatments. This checklist could include the following domains:
    - Natural history as a critical starting point - document/align on the disease baseline.
    - Trial design (RCT or not)
    - Comparator
    - Endpoints (well understood or validated)
    - Linking surrogate to patient function
    - Dose and dosing strategy.
- **Increasing pre-competitive early engagement to increase alignment.** There are opportunities for this already, but could there be scope to raise awareness of these opportunities and add capacity? Regulators, HTA agencies and payers could play a role here, alongside patients and other experts as participants in the early engagement.
- **Examining the extent of post-licensing evidence generation to support decision making.** It is unclear how much post-licensing evidence generation is happening in the rare disease space. Lessons could be learned from what is being done and how well it is working to provide evidence that can support regulatory, HTA and payer needs. CIRS could be involved in conducting this work, with input from other stakeholders.
- **Exploring the development of a structured approach to post-licensing evidence generation to increase alignment.** A checklist could potentially be developed by CIRS to refine post-licensing evidence generation to fit the multiple audiences for the evidence, with input from all stakeholders, and increase alignment of stakeholder needs. This could also explore how post-licensing evidence could support managed access agreements and dynamic pricing.
- **Exploring how to increase opportunities for early engagement by SMEs.** There may be incentives or supportive measures to help increase take-up of early engagement for SMEs who are developing rare disease treatments. Regulators and payers may play a role here.

Topic C: Utilising a life cycle approach for rare disease products to manage clinical uncertainties due to small patient populations - What are the considerations for HTA, regulators and payers?

Chair: Sharon Gorman, Director, Regulatory Intelligence and Analysis, Pfizer, UK

Rapporteur: Lucia D'Apote, Executive Director, GRR&D Policy, Amgen, Switzerland

Participants in Syndicate group C were asked to discuss different stakeholders' considerations for a life cycle approach to manage clinical uncertainties for rare disease products and to identify current tools/approaches that enable this. In addition, they were asked to discuss the challenges of using these tools/approaches and potential solutions that would help them to evolve. The following tools/approaches were identified:

Horizon scanning

There is the opportunity to harness horizon scanning to provide insights about what is known, and what is not, early on in development. There are horizon scanning efforts happening already, yet it is unclear how well they are performing and whether we have the right models, infrastructure and collaborations in place. There is concern about resources and whether horizon scanning is performed early enough; should it be earlier than two years before marketing authorisation is anticipated? Horizon scanning could also evolve away from a national and regional focus to an international one, with key agencies such as the US FDA participating. More collaboration on horizon scanning, including between regulators and HTA agencies, could also release efficiencies.

Early scientific advice

Hearing from regulators and HTA agencies early in development provides an opportunity to enhance evidence generation, yet the opportunities that exist are fragmented. New opportunities are coming through the EU Joint Scientific Consultation, which has a specific subgroup to address considerations for post-license evidence generation. However, the need for scientific advice goes beyond Europe; opportunities could arise from collaborative efforts already happening, such as the CADTH-ZIN collaboration. It is important that all stakeholders, including patients and clinicians, are routinely involved in early dialogue.

Patient registries

Registries focused on rare diseases can be a valuable source of evidence to support decision making across the life cycle. Yet they can vary across countries. This results in fragmentation; more value could be unlocked by optimising registries to provide the evidence that is needed by regulators and HTA agencies when they are first set up. Where registries already exist, it may be more appropriate to refine them than to set up additional infrastructure. Alternatively, data that is already available in mature healthcare systems, such as in the UK or Denmark, could be used if it is fit for purpose. Exploring these issues should occur around phase II and be coordinated to bring in the needs of patients, clinicians, regulators and HTA agencies.

RWD

Other forms of RWD, aside from registries, can also provide evidence to support decision making. Just as with registries though, existing databases can be limited in scope, for example, not capturing quality of life. Pragmatically, however, RWD should be considered and may add value when it comes to epidemiological data including the prevalence and incidence of rare diseases. Ongoing projects, such as Data Analysis and Real World Interrogation Network (DARWIN) EU, should be monitored.

Managed entry agreements

It is challenging to adopt a single approach to managed entry agreements (MEAs). MEAs need to be contextualised to the rare disease, for example, in terms of the length of time of the agreement. Given that they rely on data, the challenges in the data itself need to be considered, including missing data. Fundamentals of these agreements may also prove hard to agree upon; what outcome(s) should be the focus of the agreement? There is interest in whether agreements could be separated from the notion of value and used to help set a baseline and explore individual patient benefits.

Dynamic pricing

There is a need to build support at the HTA level for innovative approaches like dynamic pricing. The starting point for dynamic pricing is to identify and agree upon the key drivers of uncertainty, which can be challenging for parties to agree upon. For dynamic pricing to work in practice, there needs to be a shared understanding of what the model means. Alternative reimbursement models could be explored too; there is an opportunity to take stock of what has been tried to learn lessons. CIRS may be well placed to do this by surveying payers and companies to see what alternative reimbursement models have been utilised and how well they have worked.

Recommendations

- **Bringing together best practices for rare disease registries**. There is scope to build up examples of best practices so that they can be used as new registries are set up, or as existing registries are refined. Potential case studies could include registries for CAR-T therapies in Europe under the PRIME scheme, where there was early involvement of HTA agencies, as well as registries in use in the Netherlands.
- **Rare disease registries should be routinely considered during early engagement.** The potential need for, or the ability to refine existing registries to generate evidence to support later regulatory, HTA and payer decision making, should be discussed by all stakeholders during early engagement.
- **Explore the development of an integrated value framework**. This could consider the infrastructure needed to support evidence generation and learn from experiences in oncology, including from the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO), who have experience in terms of the infrastructure for research, development of guidelines and logistics of collaboration. Lessons could also come from existing platforms such as the International Rare Diseases Research Consortium (IRDiRC). Sandboxes could provide a safe space to support experimentation too. Lessons could be drawn from NICE's sandbox approach.

- **Evolution is needed in early scientific advice**. Companies should continue to use the opportunities that exist and work with regulators and HTA agencies to refine these dialogues over time to optimise the opportunity.
- **Transparency is needed at the HTA agency and payer interface**. Compared to the regulatory/HTA interface, the challenges at the interface between HTA agencies and payers are not well understood. Greater transparency and more payer engagement would help to provide insights on how to meet payer evidence needs and the scope for multi-stakeholder alignment on evidence. In addition, there should be more transparency about prioritisation in different healthcare systems, which involves policy makers as well as payers.
- **Exploring the development of methodological guidance for HTA for rare diseases**. Such guidance could be useful to articulate the distinct challenges for evidence generation for rare disease treatments and acceptable approaches to managing these.
- **Increase resourcing of HTA agencies**. HTA agencies can be limited in their ability to engage with stakeholders on evidence generation and throughout the assessment because of internal resource constraints. There is interest in exploring a sustainable funding model for HTA agencies so that there can be more opportunities for multistakeholder engagement.

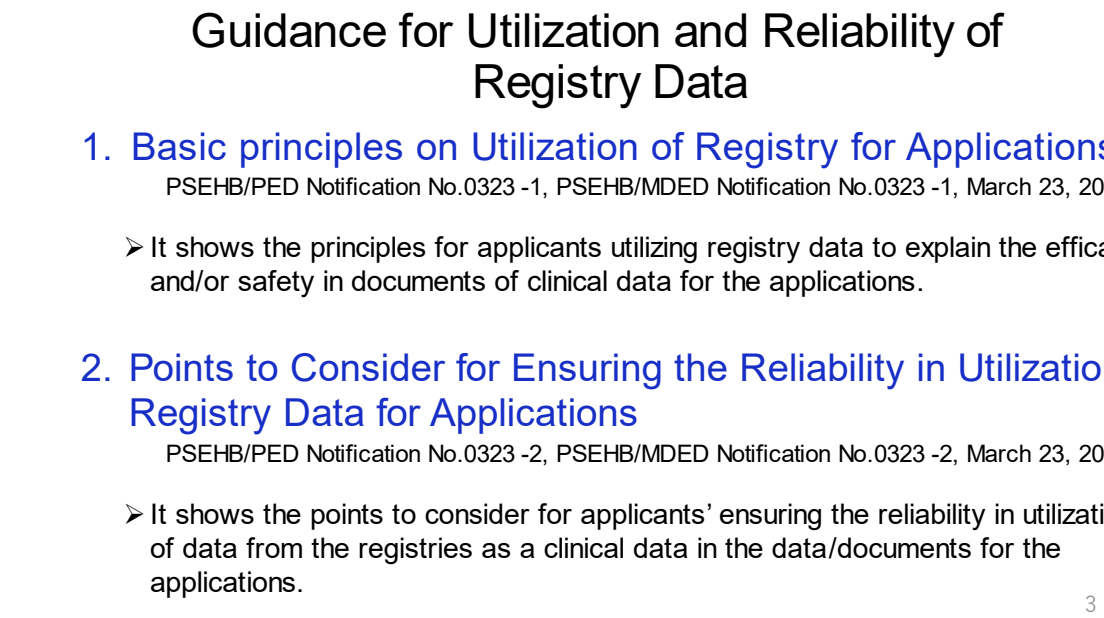
Real-world evidence for rare diseases – how should this evolve to meet the next generation of rare treatments?

Regulatory viewpoint

Dr Junko Sato, Associate Executive Director, Pharmaceuticals and Medical Devices Agency (PMDA), Japan

Support for registry owners

RWD is an enabler for more efficient development of treatments for rare diseases and at a higher scientific level. In 2021, the Ministry of Health, Labor and Welfare in Japan published two pieces of guidance on the use of RWD from registries (see slide below). The guidance provides general direction, which can be supplemented by scientific advice. There is the opportunity for advice to be given to registry holders, who are mainly drawn from the academic community, as well as advice for industry.



PMDA also provide data support. In September 2023 a new collaboration with registry holders began, the Real World Data Utilization Promotion Project; whilst it is not exclusively for rare disease treatments, it is seen as being particularly relevant to them. It includes budget support for PMDA staff to visit the organisations that host the registries and vice versa. This allows discussion on topics including quality control and assurance on reliability, key factors for using registry data to support marketing authorisation. The project will run for two years.

There is discussion, and a budget request, to support a new centre within PMDA, a Scientific Advice Centre for Paediatric and Orphan Drugs. The aim is to promote the development of treatments for children and for rare diseases, with a strengthened scientific advice system that is provided free of charge.

International research collaboration

Collaboration beyond regions and disciplines can add value to rare diseases. There can be differences at the country level, for example, concerning diagnostic criteria and biomarkers for specific rare diseases, which is why it is not just regulatory harmonisation that needs to be considered, but harmonisation in clinical practice too. Where there is greater consensus, joint data collection across countries is easier. Discussions also need to go beyond registry holders, to include patients, clinicians, regulators and others.

Registries are not the only source of evidence for rare diseases, others include electronic health records. Evidence generation should continue over the life cycle of the treatment to enable regulators to confirm the benefit-risk balance beyond market authorisation. Continuous, efficient and low-cost data collection is key.

Patient involvement

Patients have a role in engaging with regulators, as was the case with the SMA Family Association in Japan, who requested early approval of an SMA treatment. PMDA made an effort to review the product efficiently while the patient group developed a plan for post-approval data collection (if the product was approved).

Patients and their caregivers are also important sources of data, for example by submitting data from wearables and smartphones. This can be an efficient way to generate evidence and offers great potential, especially in rare diseases.

Real-world evidence for rare diseases – how should this evolve to meet the next generation of rare treatments?

HTA viewpoint

Prof Wim Goettsch, Professor HTA, Utrecht University and Special Advisor HTA, National Health Care Institute (ZIN), The Netherlands

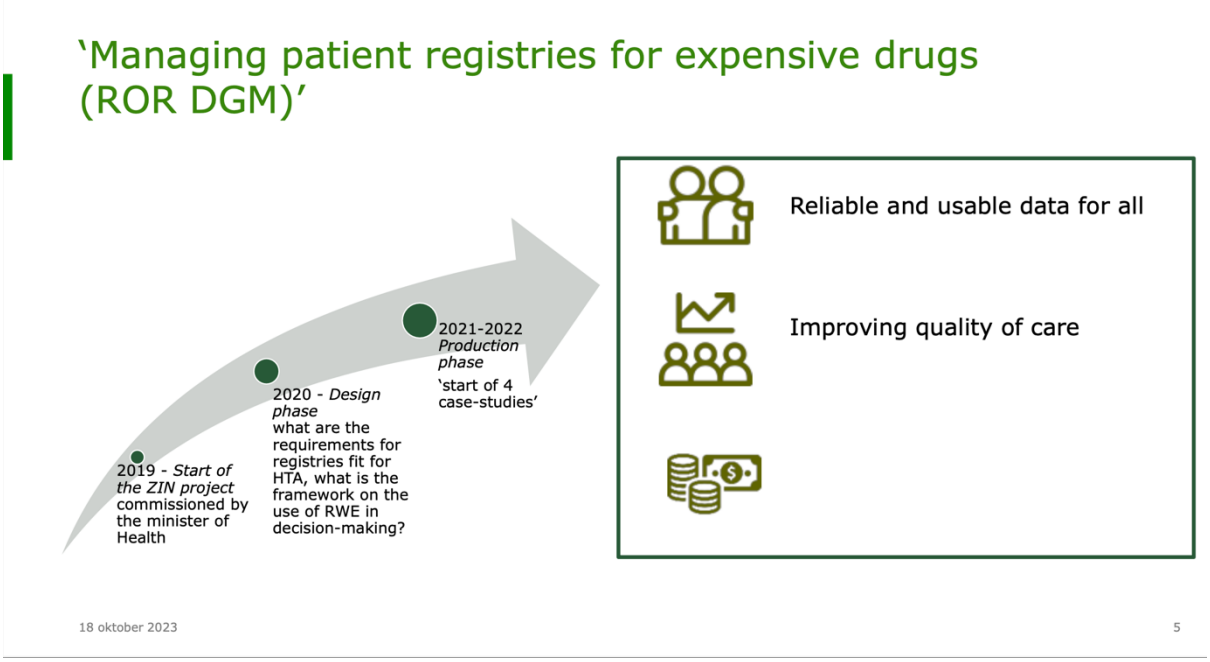
Greater uncertainty

HTA agencies are increasingly seeing treatments coming to them for evaluation that have more uncertainty about their clinical and cost effectiveness. This includes those treatments given conditional marketing authorisation. There is debate about the value of these treatments; some studies show that only 30% of these have a high therapeutic value. The evidence base for many treatments is limited, for example, some treatments given conditional marketing authorisation were authorised based on uncontrolled studies. A high proportion of such treatments will go on to receive a negative HTA recommendation or a restricted positive recommendation at best. There is recognition of the challenge of gathering evidence early on for these treatments.

Refreshed approach to managed entry

The Netherlands has experience with managed entry agreements as an approach to conditional reimbursement. Around 10 to 15 years ago, conditional reimbursement was seen as a failure. This was a result of the data not being seen as good enough, but also decision makers were reluctant to make decisions based on registry data.

There is refreshed effort to reconsider conditional reimbursement, with a focus on patient registries and other RWD sources, such as electronic health records (EHRs). Challenges persist with EHRs including missing data. There is an ongoing project, that began in 2019 – Managing Patient Registries for Expensive Drugs - to improve registries for expensive drugs, providing an opportunity to learn over time (see slide):



Part of the project included research on the status of disease-specific, as opposed to industry product-specific registries, in the Netherlands.

Four case studies are included in the project, identified via a tender, driven by criteria including being relevant to a future assessment of a hospital drug, strong support from stakeholders, especially clinicians and patients, as well as practical issues including a willingness to share anonymised individual patient-level data, in some way, with ZIN.

Libmeldy case study

A case study example is for metachromatic leukodystrophy (MLD), an ultra-rare disease that has a gene therapy called Libmeldy (atidarsagene autotemcel) available as well as other treatments. An academic-led international multi-purpose disease registry covers natural history, genotype-phenotype correlations, biomarkers, effectiveness of therapies, comparison of therapies, HTA and post-launch evidence. Having a small number of centres (one or two in a country) enables data collection for the registry. Two years were needed to set up legal agreements for data sharing between hospitals.

There is interest in bringing out lessons from this experience, to minimise the set-up challenges for future international registries. Careful consideration is needed about what data to collect. For the MLD registry, this was enabled via a Delphi approach that included multiple stakeholders so that the evidence generated could meet the needs of each. From the HTA perspective, quality of life data – specifically EQ5D – was included in data collection. There was a consideration too on the potential to use the registry data to support a pay-for-performance agreement. Work on the international registry is being leveraged as part of European Reference Network (ERN) on neurological diseases to test if there is a framework that has come from this experience that can be applied more generally.

Conclusions

A common lesson that emerged from the four case studies was the importance of defining standard data sets that all stakeholders agree to. Collecting quality of life and resource use remains a challenge. Tools like the Registry Evaluation and Quality Standards Tool (REQUEST) and the HARmonized Protocol Template to Enhance Reproducibility of Hypothesis Evaluating Real-World Evidence Studies on Treatment Effects (HARPER) are essential to support the quality and transparency of registries. Many registries can still not make use of the data that are captured in EHRs. Further international collaboration and better coordination on the collection of healthcare information at national and international levels are crucial.

Session 6: Addressing unmet needs in the next generation of rare disease: How best to enable innovation, evidence generation and patient access?

Next generation of rare disease drug policy: ensuring innovation and patient access - what needs to be considered?

Scientific advancements and regulatory policy initiatives have contributed over recent years to an increased number of approved rare disease treatments. As we move to the next generation of rare diseases, what are the key considerations to enable access within evolving health system?

Patient viewpoint

François Houÿez, Director of Treatment Information and Access, EURORDIS, France

The next generation is ultra-rare diseases

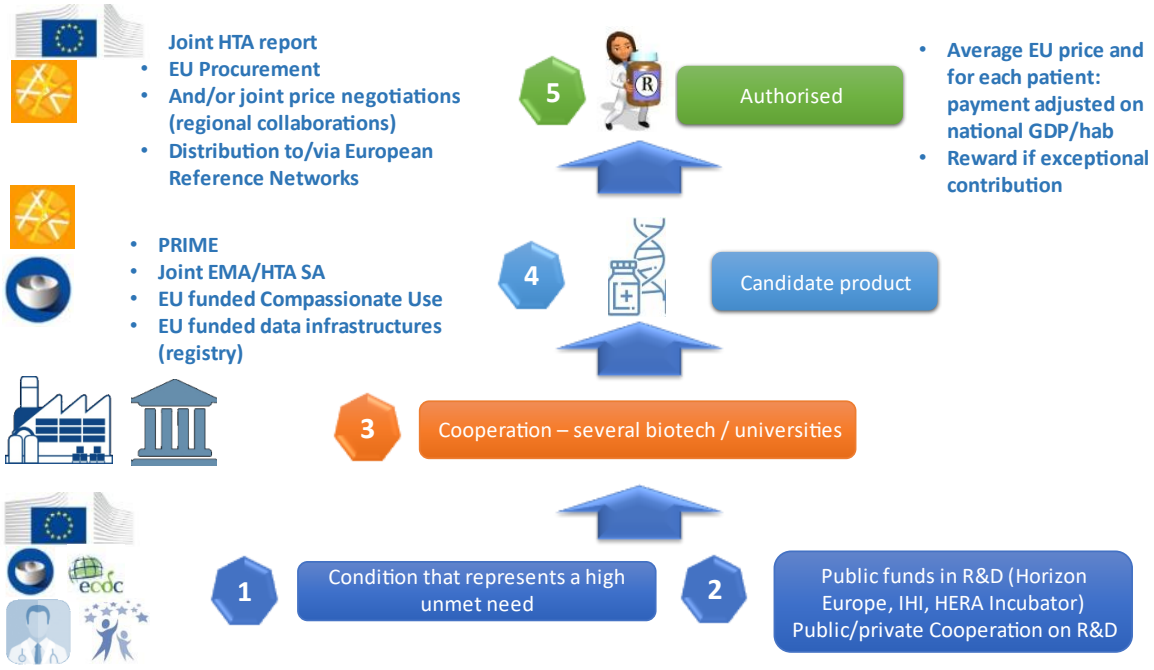
Next-generation rare diseases are those that have previously been neglected for R&D, including some ultra-rare diseases. It is estimated that 85% of rare diseases affect 1% of patients and this is where the biggest challenges remain.

Next-generation rare diseases may also be those that have been thought of as different conditions, but we are now learning that they can be different manifestations of the same genetic mechanisms. This will influence approaches to R&D, with the potential either for more salami slicing, or perhaps greater use of umbrella and basket trials.

R&D in ultra-rare diseases needs to be more cooperative

The PLUTO project from the International Rare Diseases Research Consortium (IRDiRC) is working to identify the most neglected rare diseases. A change in the approach to R&D is needed for these conditions: away from the competitive approach to a cooperative approach (see slide below).

Research grants can enable cooperative R&D from several biotechs and/or universities. Private public partnerships already exist but can be expanded. There is scope to make use of existing tools such as PRIME, joint EMA-HTA parallel scientific advice as well as European-funded compassionate use and data infrastructure, such as registries. Once a new candidate product has demonstrated safety and efficacy then a public call could support competition on price. The model starts with cooperation and then introduces competition. Joint HTA reports and European procurement would support distribution, with European price negotiation which could also allow for different prices for each country, adjusted based on GDP.


Joint HTA report
EU Procurement
And/or joint price negotiations (regional collaborations)
Distribution to/via European Reference Networks
5
Authorised
Average EU price and for each patient: payment adjusted on national GDP/hab
Reward if exceptional contribution
PRIME
Joint EMA/HTA SA
EU funded Compassionate Use
EU funded data infrastructures (registry)
4
Candidate product
3
Cooperation – several biotech / universities
1
Condition that represents a high unmet need
2
Public funds in R&D (Horizon Europe, IHI, HERA Incubator)
Public/private Cooperation on R&D

Next generation of rare disease drug policy: ensuring innovation and patient access - what needs to be considered?

Regulatory viewpoint

Karen Reynolds, Director General, Pharmaceutical Drugs Directorate, Health Canada

National strategy for rare disease

A national strategy is useful to help set the context and frame efforts to address rare diseases. The Canadian government published a new strategy in March 2023. Yet a specific approach – akin to an orphan drug designation – is not always needed within regulatory approaches. Canada is one of the few jurisdictions that does not have such a designation; instead, tools like priority review and special access programmes are applied to treatments for rare diseases. An exploration of whether an orphan drug designation may be needed found that Health Canada made similar decisions on orphan drug approvals to that of other trusted regulators. There are no plans to introduce an orphan drug designation.

Enabling clinical research

The focus in Canada is on regulatory innovation, including modernising clinical trial design. If a clinical trial is carried out in Canada, it is more likely that the treatment will be submitted for regulatory approval in Canada. Keeping up with innovation in clinical trial design is seen as in everyone's best interest. Agility in regulation is also a focus.

Domestic and international collaboration

Domestic and international collaboration are also key. Domestic collaboration is needed to enable access, with collaboration between Health Canada, HTA agencies, and health care providers within Canada. It is also recognised that equity of access needs to be addressed, given Canada's geographical size and the practicalities of patients being able to access tertiary care and clinical care centres when these tend to be in southern Canada, close to the US border.

Health Canada takes part in international collaborations, including the International Coalition of Medicines Regulatory Authorities (ICMRA), the Access Consortium and Project Orbis, which provides opportunities to inform Health Canada's work and to scale its ability to take part in work sharing. A small number of orphan drugs are included in these international collaborative efforts.

Parallel regulatory and HTA advice and aligned reviews

There are ongoing efforts to integrate evidence requirements, with evidence generation being discussed with companies via parallel regulatory and HTA scientific advice. There are also aligned reviews by Health Canada and the Canadian HTA agencies, which are helping to decrease the time from regulatory approval to HTA recommendation.

Industrial policy interacts with regulation and HTA

There remains an ongoing debate about data protection. This is not within the scope of Health Canada but is rather part of industrial policy. The broader government must understand opportunities to support work in rare disease treatments beyond regulation and HTA.

Ensuring Innovation & Patient Access: Regulatory Perspective

Canada's National Strategy for Drugs for Rare Diseases

- Designed to increase access to, and the affordability of, effective drugs for the treatment of rare diseases.

Supporting access to Drugs for Rare Diseases through:

- Established regulatory pathways
  - Priority review (180 days) or Notice of Compliance with Conditions (NOC/c) (200 days) instead of standard review (300 days); Special Access Programme
- Regulatory innovation
  - Clinical Trials Modernization; Agile licensing framework
- Increased domestic collaboration
  - Early parallel advice; Aligned reviews
- Increased international collaboration
  - ICMRA, ACCESS, Project Orbis
- Supporting mechanisms
  - Extended data protection; Fee mitigations

Next generation of rare disease drug policy: ensuring innovation and patient access - what needs to be considered?

HTA viewpoint

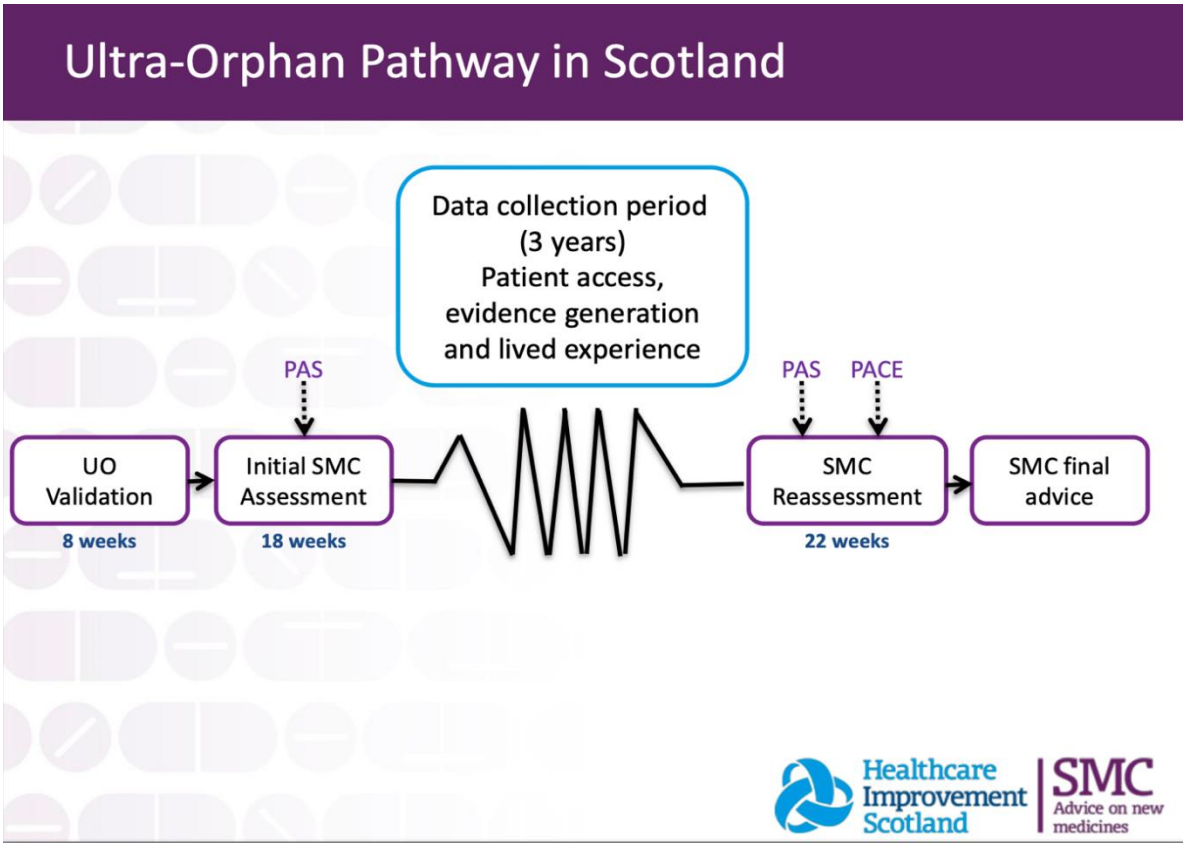
Roy Foot, Principal Pharmacist, Scottish Medicines Consortium

Different approaches for rare disease treatments

The SMC is one of the few HTA agencies with a separate framework for evaluating orphan treatments. There are additional flexibilities, including additional patient and clinician engagement (PACE). There is also a pathway for validated ultra-orphan treatments, which has specific criteria that must be met:

- The condition has a prevalence of 1 in 50,000 or less in Scotland
- The medicine has an MHRA orphan designation for the condition and this is maintained at the time of marketing authorisation
- The condition is chronic and severely disabling
- The condition requires highly specialised management.

The ultra-orphan pathway was introduced in 2018 by the Scottish government (see slide):



UO = Ultra-orphan; PAS = Patient Access Scheme; PACE = Patient and Clinician Engagement

Under the ultra-orphan pathway, the initial assessment does not make a recommendation on use, but rather identifies the strengths and weaknesses of the submission to inform evidence generation needs for the data collection period. Patient Access Schemes (PAS) are proposed by pharmaceutical companies to improve the cost-effectiveness of a medicine, often via a confidential discount on the list price, and a PAS is a requirement for entry into the initial stage of the pathway. The PACE meeting, which is conducted at the point of reassessment, is seen as particularly important, allowing patients and their carers to identify what really matters to them. Ideally, input will be sourced from patients and clinicians in Scotland with first-hand experience of the treatment. The patient experience and information that comes out of PACE meetings have been known to have a significant impact on committee opinions.

Nine medicines have gone through the first stage of the ultra-orphan pathway so far. The first treatments are now coming back for reassessment. The Scottish Government agrees the data collection plan with the pharmaceutical company. While it may be desirable to revisit HTA decisions at a later stage, it is recognised that reassessment has the potential to pose capacity challenges for relatively small HTA agencies like SMC.

Enabling access going forward

SMC expects the next generation of rare disease treatments to be even more complex from an HTA perspective, with greater clinical and economic uncertainty. This may require an increasing reliance on data types and sources (accepting generalisability limitations), as well as ensuring that the patient voice is captured. It will become more important to try to enable real-world data to be integrated into HTA (supplemental evidence) in a consistent way that is acceptable to all stakeholders. There is also a need for exploration of innovative pricing mechanisms to help address the uncertainty.

Next generation of rare disease drug policy: ensuring innovation and patient access - what needs to be considered?

Company viewpoint

James Ryan, Global Director, HTA Policy, AstraZeneca, UK

R&D in rare disease treatments is risky and evidence generation costly

It is important to remember that the end goal is patient access. Yet there are challenges to achieving this, spanning from discovery through to delivery of the treatment to patients. From a company perspective, greater predictability is needed given that R&D in rare diseases is a risky investment, even more so when developing for ultra-rare diseases. Companies want to know the goalposts and whether they will likely change in ten years. Everyone agrees evidence is valuable, however, it must be evidence that will impact decision making given the cost of its generation. Companies want support to help them generate valuable evidence from the perspective of regulators, HTA agencies and payers.

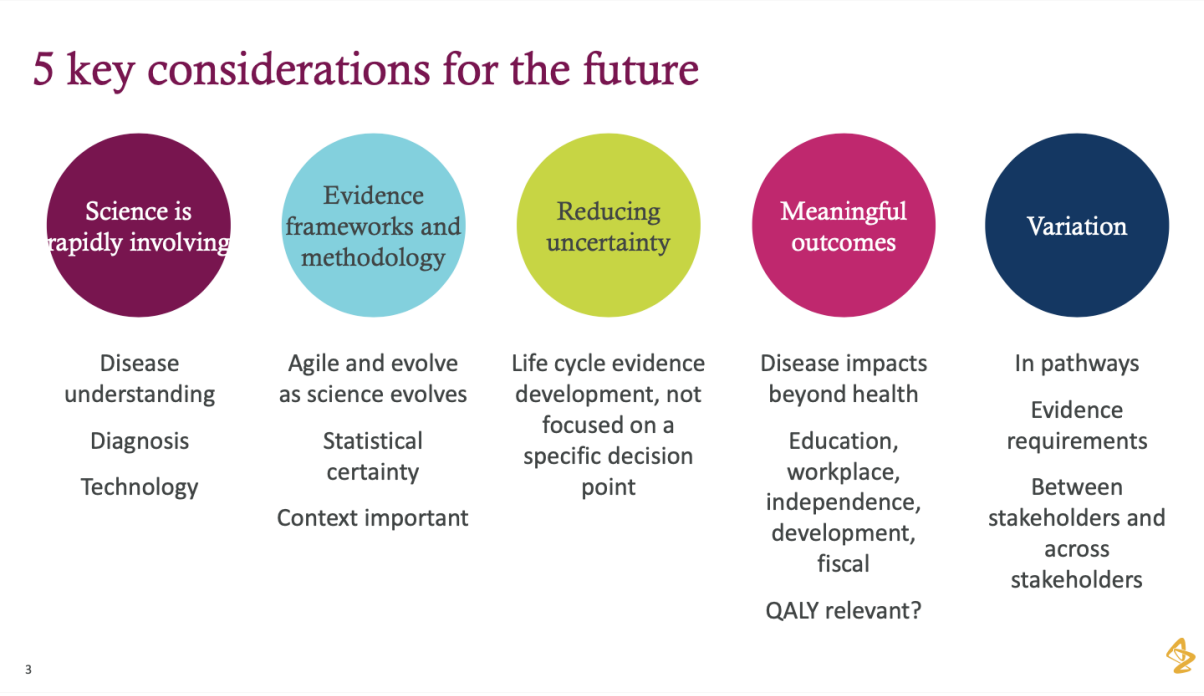
Uncertain impact of changing current incentives

Changing current incentives for the development of rare disease treatments could potentially decrease the number of treatments coming to market. The European Federation for the Pharmaceutical Industry Association (EFPIA) has estimated that the proposed draft of EU pharmaceutical legislation would discourage the development of up to 45 rare disease treatments in the EU by 2035.

Incentives need to be looked at in the round

Investment in treatments for rare diseases is driven by a variety of factors. A lack of investment, as has been highlighted by EFPIA, is the cumulative impact of scientific regulatory policy and economic barriers, compounded by uncertainties in pricing and reimbursement. Given that it's a whole system that drives investment, it follows that a multi-stakeholder approach is needed, supported at the government level.

There are key considerations for the future of rare disease drug policy (see slide):



QALY = Quality Adjusted Life Years

Early multi-stakeholder engagement is key

For the future, early multi-stakeholder scientific advice is seen as the foundation for future patient access, with meaningful engagement throughout the life cycle. Prioritisation and harmonisation on evidence needs is key, but also at times, there will be a need to compromise. Contextualisation and methods that can reduce uncertainty are needed. Evidence development must adopt a life cycle approach and not be a one-off activity.

Next generation of rare disease drug policy: ensuring innovation and patient access - what needs to be considered?

Academic viewpoint

Prof Lotte Steuten, Deputy Chief Executive, Office of Health Economics (OHE), UK

The impact of next-generation rare diseases is uncertain

Next-generation rare disease treatments are likely to be targeted, and personalised, for example cell and gene therapies. They may also be treatments used in multiple indications and in combination. Their economic impact will be related to whether the health gains are primarily driven by an increase in length of life or improvement in quality of life. For example, a therapy that addresses the root cause of a disease with early mortality may substantially increase length of life, which has low-cost offsets to health care systems but high value to society. Whereas a therapy that reduces morbidity and improves quality of life has the potential to generate cost savings to the health care system and a high value to society too.

Changing incentives could risk innovation

There is a concern that changes proposed to EU regulation are at odds with innovation, such as the EU draft Pharmaceutical Legislation but also the In Vitro Diagnostic Medical Device Regulation (IVDR). There may also be ripple effects from the Inflation Reduction Act (IRA) in the US too, which is predicted to disproportionately affect rare diseases because, whilst orphan-designated treatments are exempt, follow-on indications are not. This can be seen as a rebalancing of incentives by some, or it may counteract a decade of progress. Time will tell.

Next generation HTA

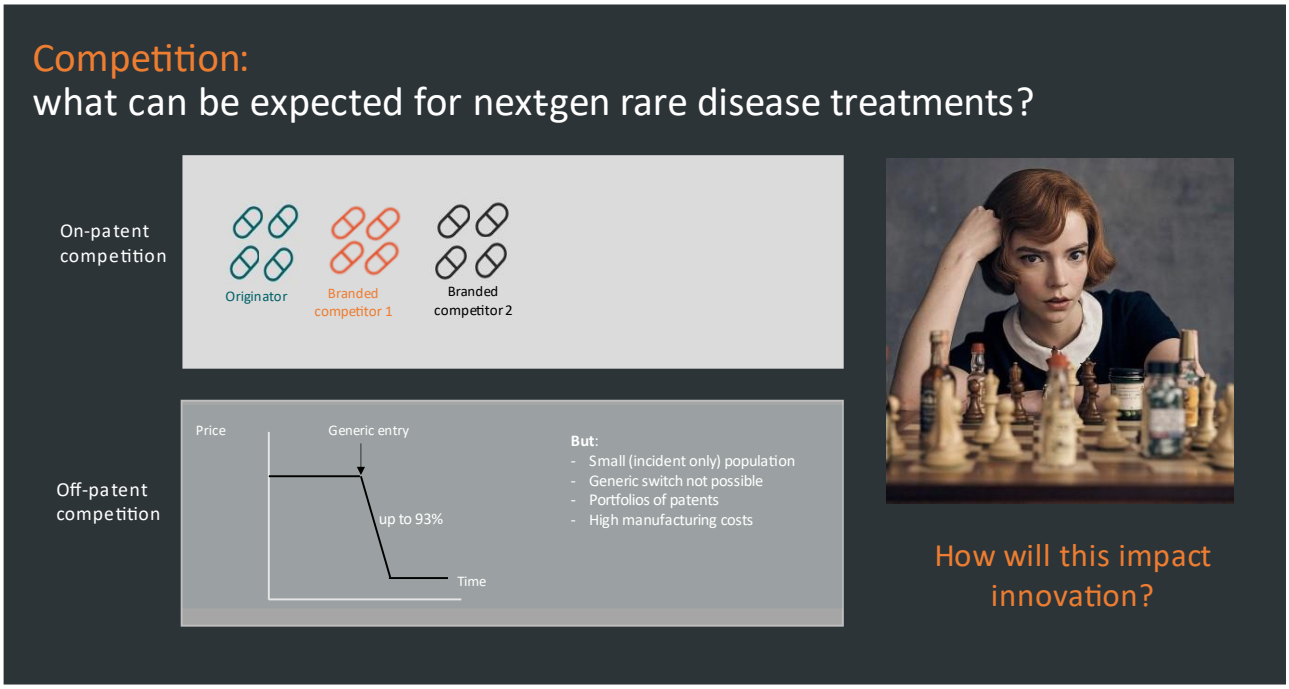
Next-generation rare disease treatments require next-generation HTA. This should recognise that more data does not always mean less uncertainty. There is also a need to address questions like when is a cure a cure? There will be more tension in the future between value-based prices and affordability, yet this is a financing problem, not an economic one.

Fit-for-purpose payment models

More work is needed to explore the role of performance-based risk-sharing agreements, which may be hard to do but are much needed. In doing so, it is important to keep in mind what specific problem these agreements are aiming to solve and ensure that the payment chosen is fit for purpose. Novel payment models like volume-delinked subscription models, which are being trialled for antibiotics, are an example.

The impact of competition is uncertain

The extent of competition and its potential impact on prices and future innovation is uncertain. Generally, the expectation is that there is very little room for competition in rare diseases because the target populations are so small, and particularly in the case of one-off treatments, once the prevalence population is treated, there is only the incident population left. However, there have been cases already where there are competitors to one-off treatments. The effect on price will be driven by the type of competitor product and its cost-effectiveness analysis.



Next generation of rare disease drug policy: ensuring innovation and patient access - what needs to be considered?

Payer viewpoint

Dr Detlev Parow, Former Head, Department of Medicines, Medical Remedies and Selective Contracts, DAK – Gesundheit, Germany

Budget impact cannot be ignored

The next generation of drug policy can be taken by some to mean a price increase. Politicians have made promises in the past about the proportionate contribution to social insurance; in 2021 the former German government promised to keep social insurance contributions below 40%. Now, in 2023, it is 40.8%. That means that it is no longer the payer's willingness to pay; it is the societal willingness to pay that needs to be considered, because either the contribution rate has to increase or taxes increase.

Rare diseases are not rare when you consider all of them together. With rising prices, orphan drug spending becomes an ever-increasing proportion of total health care spend. This is not sustainable. There is also a “lawful fiction’ that all orphan drugs have an added benefit because of the design of the German system for assessing drugs; in practice not all do, based on assessments that have taken place once orphan drugs have breached a budget impact threshold.

Access varies across Europe

Evidence on the availability of orphan drugs has shown variability across Europe. This may be related to HTA approaches, to willingness and ability to pay, as well as company strategy around target markets.

New payment and financing models needed

It would be better not to privilege orphan drugs at the HTA level; instead, it should be at the stage of price negotiations. Prices should be reduced too. Prescriptions bring revenue, not the price. New payment models are needed, with interest in dynamic pricing that could go both ways (i.e. higher prices for more effective treatments, lower prices for less effective treatments, and if found not to be effective, the price should be zero).

Funding sources are also needed. If there is a political desire to fund orphan drugs, then extra funds should be given to the healthcare system through an approach like the UK Cancer Drugs Fund. If there is a desire for equality across the EU, it follows that there should be joint EU procurement for orphan drugs.

Ensuring innovation and patient access: What needs to be considered

- **Stop the orphan privilege at HTA level – face the evidence available**

  If we want to privilege orphan drugs (ODs) – not on HTA level but at the level of price negotiations

- **Reduce prices!**

  295.000 / 390.000 / 540.000 p.a. are no tolerable price levels – only to discuss how to pay is not sufficient, we need new payment models (dynamic pricing)

- **Different source of funding for ODs ("Cancer Drug Fund"-like)**

  If priority for ODs is politically intended, it needs an extra budget for funding

- **Equal health conditions in all EU countries – Joint EU procurement for ODs**

  In exceptional circumstances, EU procurement can be a contribution to a harmonised EU OD access, availability and reimbursement.

Summary of discussion from Session 6

Next-generation rare diseases

Next-generation rare diseases have not been formally defined. There is a sense that the 'low hanging fruit' has been addressed already, such as those rare diseases where an enzyme replacement therapy can be used to treat them. The next generation can be thought of as those that use newer technologies, gene therapies for example.

Political choices

Allocation to health care vs other areas of government spending is a political choice. Prioritisation has to happen and there are external challenges that governments have to respond to, such as the Ukraine war.

Interest in different models of commercialisation and production

There is interest in different models, such as the 'collaboration first, competition second' proposal from EURORDIS, but also in exploring whether hospitals could produce some treatments, such as CAR-T therapies. In essence, it's about allowing for different models according to the rare disease context.

Company decision making

Commercial company decision making about which rare disease areas to focus on is complex. Science and commercialisation feature. Treatments are brought to market even knowing that commercialisation will be challenging because there is the potential to address unmet needs. Cross-subsidisation can help counter commercial challenges in multiple product companies.

Priority early engagement

There was interest in exploring whether a priority service could be offered where HTA provide early advice to companies. This could even be used to help companies decide which treatments not to develop further. Patient groups already do their own prioritisation and focus on supporting the development of treatments that they see as most promising. Their perspectives could be part of early engagement. Priority position for HTA is given already through the Innovative Licensing and Access Pathway (ILAP) in the UK with NICE and SMC.

Competition

To help manage sustainability, competition must not be overlooked. The degree of competition is difficult to predict in the case of gene therapies.

Appendix

List of workshop attendees

Affiliations are stated as they were at the time of the meeting.

Dr Tatsiana Audzevich	Senior Manager, EU Regulatory Affairs	**Amgen, UK**
Dr Indranil Bagchi	VP Global Pricing and Market Access Head	**GlaxoSmithKline, USA**
Jo Bailey	Global Pricing & Market Access Director	**GlaxoSmithKline, UK**
Simon Bennett	Director, Regulatory Policy	**Biogen, UK**
Dr Kate Betteridge	Senior Director, Global Regulatory Portfolio Lead, Rare Disease	**Pfizer, UK**
Dr Camilla Birkegård	Department Manager	**Novo Nordisk, Denmark**
Dr Claus Bolte	Chief Medical Officer	**Swissmedic**
Dr Magda Bujar	Senior Manager, Regulatory Programme and Strategic Partnerships	**CIRS**
Thomas Butt	Executive Director, Head of Global Health Economics & Outcomes Research	**BioMarin, UK**
Patricia (Trish) Caetano	Director, Drug Data Services and Analytics	**CADTH, Canada**
Stephane Callewaert	Director - EMEA Policy Lead, Global Regulatory Policy & Intelligence	**Janssen, Belgium**
Dr Nick Crabb	Interim Director, Science, Evidence and Analytics	**National Institute for Health and Care Excellence (NICE), UK**
Dr Jayne Crowe	CHMP Member	**Health Products Regulatory Agency, Ireland**
Lucia D'Apote	Executive Director, GRR&D Policy	**Amgen, Switzerland**
Cecile De Coster	Executive Director, GRA DS	**Alexion, Switzerland**
Dr Lode Dewulf	Independent Director and Consultant	**Corvalus, Belgium**
Dr Sahar Barjesteh van Waalwijk van Doorn-Khosrovani	Member of the National Funder's Committee for Evaluation of Specialised Medicines and Companion Diagnostics	**CZ; Affiliated with Leiden University Medical Centre, The Netherlands**
Prof Hans-Georg Eichler	Consulting Physician	**Association of Austrian Social Insurance Institutions**
Roy Foot	Principal Pharmacist	**Scottish Medicines Consortium, UK**
Dr Ramiro Gilardino	Global HTA Policy Leader	**MSD, Switzerland**
Prof Wim Goettsch	Professor HTA of Pharmaceuticals, WHO Collaborating Centre for Pharmaceutical Policy and Regulation	**Utrecht University, The Netherlands**

Sharon Gorman	Director, Regulatory Intelligence and Analysis	**Pfizer, UK**
Dre Michele de Guise	President and CEO	**INESSS - National Institute for Clinical Excellence in Health and Social Services, Canada**
Dr Michael Happich	Senior Director VEO International	**Eli Lilly, Germany**
Dr Adam Heathfield	Access Innovation	**Pfizer, UK**
Niklas Hedberg	Chief Pharmacist	**TLV, Sweden**
Gill Hepton	Administrator	**CIRS**
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François Houÿez	Director of Treatment Information and Access	**EURORDIS – Rare Diseases Europe, France**
Dr Li Ying (Grace) Huang	Director	**Division of Health Technology Assessment, Center for Drug Evaluation, Taiwan**
Assoc. Prof. Wanrudee Isaranuwatchai	Director	**Health Intervention and Technology Assessment Program, Thailand**
Dr Ruth Pulikottil-Jacob	Head, Global Health Economic & Value Access Rare Diseases	**Sanofi, UK**
Mohit Jain	VP, Value, Access and Strategic Pricing, Global Head	**BioMarin, UK**
Dr David Jefferys	Senior Vice President	**Eisai, UK**
Therese Karstensen	EU Regulatory Lead	**LEO Pharma, Denmark**
Alastair Kent	Independent Patient Advocate	**UK**
Emma Kent	Policy, Value and Access Partner	**Roche, UK**
Adem Kermad	Senior Analyst	**CIRS**
Dr David King	Director Regulatory Intelligence	**Regeneron, UK**
Prof Finn Børlum Kristensen	Professor	**University of Southern Denmark, Danish Centre for Health Economics**
Juan Lara	Senior Research Analyst	**CIRS**
Dr Carlos Martín-Saborido	Advisory member General Directorate of the Common Portfolio of SNS and Pharmacy Service	**Ministry of Health, Spain**
Hon Prof Andrew Mitchell	Honorary Professor, Department of Health Economics Wellbeing and Society	**The Australian National University, Australia**
Anderson Vezali Montai	Executive Manager, Biological Products Office	**ANVISA, Brazil**
Dr Judith Nelissen	Head HEOR	**Astellas, The Netherlands**
Dr Brian O'Rourke	Chair	**CIRS HTA Steering Committee**

Dr Magdalini Papadaki	Executive Director, Regulatory Affairs International	**MSD, UK**
Dr Detlev Parow	Former Head, Department of Medicines, Medical Remedies and Selective Contracts	**DAK – Gesundheit, Germany**
Susana Pereira	Associate Director, Regulatory Affairs	**Regeneron, UK**
Marie-Pierre Petit Jean	Europe Regulatory Expert Head	**Sanofi, France**
Marguerite Prévotat	Vice President, Head of Global Regulatory Affairs Rare Diseases	**Ipsen, France**
Karen Reynolds	Director General, Pharmaceutical Products Directorate	**Health Canada**
Laura Roden	Associate Director, Europe Regulatory Affairs	**AbbVie, UK**
James Ryan	Global Director, HTA Policy	**AstraZeneca, UK**
Dr Junko Sato	Associate Executive Director	**Pharmaceuticals and Medical Devices Agency (PMDA), Japan**
Dr Vanessa Schaub	Head, Global & European HTA Strategy	**F. Hoffmann La Roche, Switzerland**
Dr Anja Schiel	Special Adviser, Lead Methodologist in Regulatory and Pharmacoeconomic Statistics	**Norwegian Medicines Agency, Norway**
Adj Prof John Skerritt	Adjunct Professor, and Chair, Scientific Advisory Council, CIRS	**University of Sydney, Australia**
Dr Belen Sola	Research Analyst	**CIRS**
Anna Somuyiwa	Head	**CIRS**
Prof Lotte Steuten	Deputy Chief Executive	**Office of Health Economics, UK**
Dr Henrik Svedsater	Value Evidence & Outcomes Director	**GlaxoSmithKline, UK**
Prof Steffen Thirstrup	Chief Medical Officer	**European Medicines Agency**
Prof Adrian Towse	Emeritus Director & Senior Research Fellow	**Office of Health Economics, UK**
Dr Sean Tunis	Principal	**Rubix Health, USA**
Prof Stuart Walker	Founder and Senior Consultant	**CIRS**
Dr Tina Wang	Senior Manager, HTA programme and Strategic Partnerships	**CIRS**
Lara Wolfson	AVP & Head of HTA Statistics	**MSD, Switzerland**
Dr Durhane Wong-Rieger	President and CEO	**Canadian Organization for Rare Disorders**
Dr Songmei Xie	Director of Clinical Department Center for Drug Evaluation,	**National Medical Products Administration (NMPA), China**
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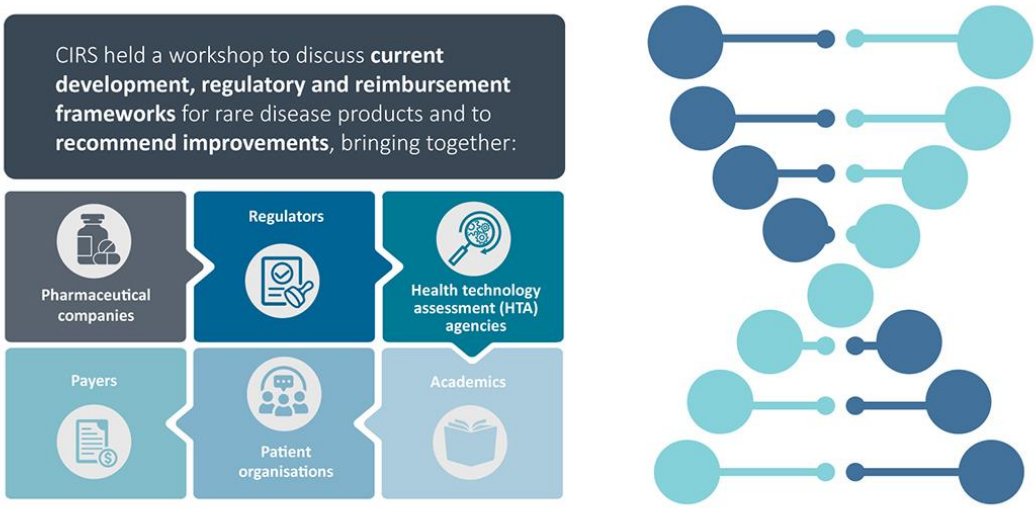
Infographic summary



Workshop recommendations

Evolving incentives

Explore different incentive models for **treatments for ultra-rare diseases**

Investigate which regulatory and HTA approaches improve the probability of **successful review and reimbursement**

Leverage learnings from **managed entry agreements**

Improve evidence development

Multi-stakeholder engagement
Earlier/more opportunities

Shift mindsets on patient input
Reduce perception that patients who work with industry have a conflict of interest when interacting with regulatory/HTA agencies

Develop structured checklists for pre-/post-licensing evidence generation
Increase alignment on stakeholder needs

Better manage uncertainty

Rare disease registries
Establish best practice

Rare disease products
Develop integrated value framework utilising research and an experimental 'sandbox' approach

Rare disease space
Examine the extent of post-licensing evidence generation; how much is happening and what is working well?

About CIRS

The Centre for Innovation in Regulatory Science is a neutral, independent UK-based subsidiary of Clarivate plc. Its mission is to maintain a leadership role in identifying and applying scientific principles for the purpose of advancing regulatory and Health Technology Assessment policies and processes. CIRS provides an international forum for industry, regulators, HTA bodies and other healthcare stakeholders to meet, debate and develop regulatory and reimbursement policy through the innovative application of regulatory science. It is governed and operated by Clarivate for the sole support of its members' activities. The organisation has its own dedicated management and advisory boards, and its funding is derived from membership dues, related activities, and grants.

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