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

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WORKSHOP SYNOPSIS

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CIRS Centre for Innovation in Regulatory Science

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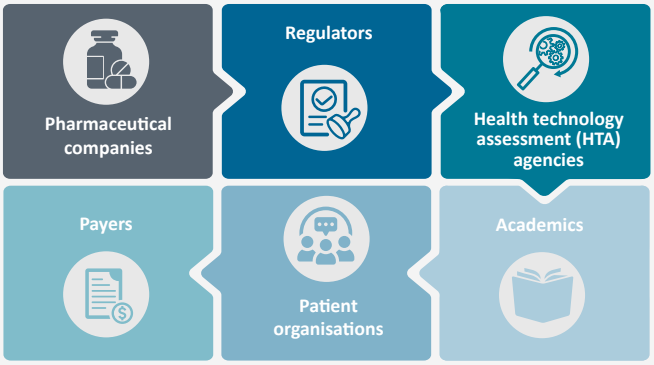
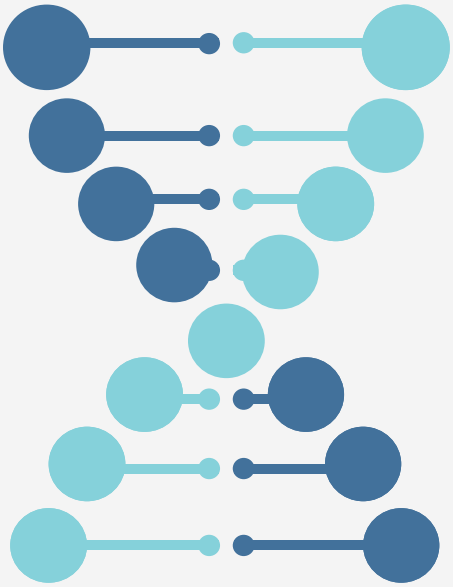
Improving development, regulatory and reimbursement frameworks for rare disease products

CIRS held a workshop to discuss **current development, regulatory and reimbursement frameworks** for rare disease products and to **recommend improvements**, bringing together:





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?

Background

There are an estimated 300 million people across the world affected by around 7,000 known rare diseases. Challenges in bringing treatments to market for these conditions include small patient populations, which make randomised controlled trials (RCT) difficult to conduct, and the frequent need for companion diagnostics. Alternative sources of evidence – including real world evidence (RWE) – are often used to support regulatory approval and health technology assessment (HTA) submissions for rare disease treatments. The acceptability of this evidence varies across countries and between regulatory and HTA agencies.

Incentives for research and development (R&D) for rare disease treatments have been in place for over 20 years in jurisdictions including Europe and the US. These include a period of market exclusivity and a range of support from regulatory agencies. CIRS data shows that the number of new treatments with an orphan drug designation given regulatory approval has increased over time, suggesting that incentives have encouraged R&D. With uncertainty in the evidence base for many of these orphan drugs, there is a challenge for HTA agencies to be able to recommend orphan drugs and for payers to fund them. Some, but not all HTA agencies, have tailored approaches when assessing orphan drugs.

The European Commission (EC) is conducting a general reform of the legislative framework for the pharmaceutical industry, including modifications for orphan drugs incentives. Coupled with the new EU HTA Regulation, it is timely to evaluate the review and reimbursement frameworks for rare disease treatments and to explore the potential for improvements.

In this workshop, CIRS brought together senior representatives from the international pharmaceutical industry, regulatory agencies, HTA agencies, payers, patient community and academia to identify challenges and opportunities for adapting regulatory or reimbursement frameworks for rare disease products, and to develop recommendations on how these can improve to best support stakeholder evidence needs.

Workshop sessions

This multi-stakeholder workshop consisted of a series of presentation sessions and three parallel breakout discussions. Presentations explored trends in regulatory and HTA approvals of orphan products and perspectives on incentives for rare disease treatments, fitness of today's tools to address uncertainty, the potential for a life cycle approach for evidence generation, the role of multiple stakeholders in reimbursement decision making, the evolution of RWE and considerations for the next generation of rare disease treatments.

The breakout groups were asked to examine three topics when considering evidence generation to support financially sustainable access to rare disease products:

- **Incentives from a policy and practice perspective –** Do current incentives need to evolve for the development, review and reimbursement of rare diseases?
- **Evidence development for regulators and health technology assessors for rare disease products –** How best to address and align the needs of regulators and HTA agencies?
- **Life cycle approach for rare disease products to manage clinical uncertainties due to small patient populations –** What are the post-approval considerations for HTA agencies, regulators and payers?

Key points from presentations and open-floor discussions

Enhanced collaboration is vital in evidence generation

Getting better at working together was seen by all as a pre-requisite to refining today's approaches to evidence generation; that ranges from collaboration by pharmaceutical companies to identify what is important to patients and carers, to running clinical studies and horizon scanning, all the way through to multiple perspectives being brought to bear on regulatory, HTA and payer decision making on rare disease treatments.

Collaboration is even more important for the ultra-rare diseases. Early engagement on evidence generation, not just for initial regulatory, HTA and payer decisions, but across the life cycle, is part of the collaborative ethos. Patients should be involved in these discussions, though this can create perceptions of conflict of interest, which needs to be managed more proactively. Yet opportunities for such engagement, for example, via early scientific advice, can be limited by resource constraints, on both agency and company sides, and are not always able to generate a consensus and predictability in terms of acceptable evidence to support decisions in the future.

Greater predictability would be welcome to the industry, alongside further alignment in regulatory, HTA and payer requirements. The interface between HTA agencies and payers could be an area of focus for the future to ensure timely implementation of HTA recommendations and patient access. There may be a need to increase resources for regulators and HTA agencies to enable them to deliver earlier, and more, engagement opportunities.

Incentives matter

Current regulatory incentives have led to more rare disease treatments coming to market. However, there is concern that these are not well balanced; there are orphan drug blockbusters and at the same time, many neglected rare diseases. There is also the issue of 'salami slicing', where diseases are divided to create rare subgroups and incentives can be received for each new indication. The EC has proposed changes to incentives for rare disease treatments, but there is concern amongst industry that they could risk a reduction in development for future treatments. This would suggest caution is needed in the pursuit of reforms to orphan drug incentives.

Debate on reform could even consider changing the terminology; is 'support' for rare disease treatments a communications shift that could enable more collaboration by reducing the politics that can be generated with the term 'incentive'? Regulatory incentives are not the only incentives in play, with competition in the market influencing pricing and spending on orphan drugs. Perceived high prices and budget impact, with small patient numbers for individual rare diseases adding up as more rare disease treatments come to market, are a concern to some in the HTA and payer community.

Managing uncertainty must be seen as an ongoing activity

Managing uncertainty is applicable to all stages of the life cycle of a rare disease treatment. Requirements for evidence generation can be shaped by multiple regulators, HTA agencies and payers coming together to focus on the most important common issues, considering both RCTs and RWE.

There is scope to leverage lessons from managed entry agreements – also known as risk-sharing, performance-based, and outcome-based, agreements – so that stakeholders can identify what types of agreements are worth pursuing given the resources required to deliver them. There is interest in exploring dynamic pricing, although there is a need for a multistakeholder consensus on what the model means in practice. Whilst patient access is rightly a focus, exit from such agreements is a difficult but necessary consideration too.

Stakeholders are thinking about how to go global for evidence generation

That presents a variety of challenges, including how to fund and operationalise such an approach given the need to work through legal, funding and interoperability issues, as well as build on what is already available, for example through existing registries. Global evidence generation offers the promise of more robust evidence that would benefit decision making across companies, regulators, HTA agencies and payers. Clinicians and patients too have an interest in evidence that supports their treatment decision making. Patient access should also be thought of in global terms; how can stakeholders work together to enable access for patients in low and middle-income countries, as well as those in high-income countries?

Reforming today's approaches to rare disease treatments is not easy but sandboxing could help

Making changes to incentives and approaches to regulatory, HTA and payer decision making may be hard to implement given vested interests and the unpredictable impact of proposals from the EU pharma legislation. Sandboxes to develop shared reform proposals and explore them in a safe environment could be used more often and offer a learning-by-doing opportunity to stakeholders.

There is interest in more radical changes

Some are calling for more radical changes rather than small changes to current incentives, such as adjusting timelines for market exclusivity. Whilst not applicable to every rare disease, there could be a 'collaboration first, competition second' model for development and commercialisation, using a mix of public and private funds to develop treatments for extremely rare disease areas with high unmet needs. By making use of today's tools, such as the PRIME designation, but also building in more collaborative approaches like joint EU procurement, new treatment breakthroughs could be made, but also be more sustainable for healthcare systems.

Success is sustainable patient access

Reforms to any part of the pathway for rare disease treatments must be judged by what matters most to patients and their carers: access to rare disease treatments that meaningfully address their needs. They must also be judged in terms of sustainability to society.

Recommendations from breakout discussions

Policy and practice perspective – do current incentives need to evolve for the development, review, and reimbursement of rare diseases?

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 already 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 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.

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?

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) PARADIGM project, Council for International Organizations of Medical Sciences (CIOMS) Working Group XI and EURORDIS. Education and awareness 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 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's 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 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 ways to help increase take-up of early engagement for SMEs who are developing rare disease treatments. SMEs often face greater capacity constraints than larger companies for such activity.

Life cycle approach for rare disease products to manage clinical uncertainties due to small patient populations – What are the post-approval considerations for HTA, regulators and payers?

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 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 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 the logistics of collaboration. Lessons could also come from existing platforms such as International Rare Diseases Research Consortium (IRDiRC). Sandboxes could be used to 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 as to how to meet payer decision criteria and the scope for multi-stakeholder alignment on evidence.

Exploring the development of methodological guidance for HTA for rare diseases

These 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 their internal resource constraints. There is interest in exploring those resource constraints and explore the opportunities to resource HTA agencies to enable them to engage with multiple stakeholders.

Workshop programme

Session 1: Addressing unmet needs for identification and development of rare disease products: How best to enable innovation?	**Session 2:** Evidence generation during development of rare disease products – What are the considerations to improve predictability?
Chair: Dr Brian O'Rourke, Chair, CIRS HTA Steering Committee	**Chair: Dr Brian O'Rourke**, Chair, CIRS HTA Steering Committee
Dr Tina Wang, Senior Manager, HTA programme and Strategic Partnerships, CIRS	**Alastair Kent,** Independent Patient Advocate, UK
Martine Zimmerman, Senior Vice President, Head of Regulatory and Quality R&D, Ipsen, France	**Dr Anja Schiel,** Special Adviser, Lead Methodologist in Regulatory and Pharmacoeconomic Statistics, Norwegian Medicines Agency (NoMA)
François Houÿez, Director of Treatment Information and Access, EURORDIS, France	**Andrew Mitchell,** Honorary Professor, Department of Health Economics Wellbeing and Society, The Australian National University, Australia
Dr Jayne Crowe, CHMP Member, Health Products Regulatory Agency, Ireland	**Mohit Jain,** VP, Value, Access and Strategic Pricing, Global Head BioMarin, UK
Niklas Hedberg, Chief Pharmacist, TLV, Sweden	**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
Session 3: Addressing regulatory and HTA needs at the time of assessment and post-approval – What strategies, methodologies and activities can be used?	**Session 4:** Syndicate discussions
Chair: Prof Hans-Georg Eichler, Consulting Physician, Association of Austrian Social Insurance Institutions	**Syndicate A) Incentives for the development, review, and reimbursement of rare diseases**
Dr Ramiro Gilardino, Global HTA Policy Leader, MSD, Switzerland	**Chair: Dr Sean Tunis,** Principal, Rubix Health, USA
Dre Michele de Guise, President and CEO, National Institute for Clinical Excellence in Health and Social Services (INESSS), Canada	**Rapporteur: Stephane Callewaert,** Director – EMEA Policy Lead, Global Regulatory Policy & Intelligence, Janssen, Belgium
Dr Claus Bolte, Chief Medical Officer, Swissmedic	**Syndicate B) Evidence development for regulators and HTA of rare disease products**
Dr Durhane Wong-Rieger, President and CEO, Canadian Organization for Rare Disorders, Canada	**Chair: Prof Adrian Towse,** Emeritus Director & Senior Research Fellow, Office of Health Economics, UK
Dr Nick Crabb, Interim Director, Science, Evidence and Analytics, National Institute for Health and Care Excellence (NICE), UK	**Rapporteur: Dr Kate Betteridge,** Global Regulatory Portfolio Lead, Pfizer, UK
Dr Carlos Martin, Advisory member, General Directorate of the Common Portfolio of SNS and Pharmacy Service, Ministry of Health, Spain	**Syndicate C) Life cycle approach for rare disease products to manage clinical uncertainties**
Dr Ruth Pulikottil-Jacob, Head, Global Health Economic & Value Access Rare Diseases, Sanofi, UK	**Chair: Sharon Gorman,** Director, Regulatory Intelligence and Analysis, Pfizer, UK
Dr Detlev Parow, Former Head, Department of Medicines, Medical Remedies and Selective Contracts, DAK – Gesundheit, Germany	**Rapporteur: Lucia D'Apote,** Executive Director, GRR&D Policy, Amgen, Switzerland
Session 5: RWE for rare diseases – how should this evolve to meet the next generation of rare disease treatments?	**Session 6:** Addressing unmet needs in the next generation of rare disease: How best to enable innovation, evidence generation and patient access?
Chair: Adjunct Prof John Skerritt, University of Sydney, Australia	**Chair: Prof Steffen Thirstrup,** Chief Medical Officer, EMA
Dr Junko Sato, Associate Executive Director, Pharmaceuticals and Medical Devices Agency (PMDA), Japan	**François Houÿez,** Director of Treatment Information and Access, EURODIS, France
Prof Wim Goettsch, Professor HTA, Utrecht University and Special Advisor HTA, National Health Care Institute (ZIN), The Netherlands	**Karen Reynolds,** Director General, Pharmaceutical Drugs Directorate, Health Canada
	Roy Foot, Principal Pharmacist, Scottish Medicines Consortium
	James Ryan, Global Director, HTA Policy, AstraZeneca, UK
	Prof Lotte Steuten, Deputy Chief Executive, Office of Health Economics, UK
	Dr Detlev Parow, Former Head, Department of Medicines, Medical Remedies and Selective Contracts, DAK – Gesundheit, Germany

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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