A cooperative process to reach mutually acceptable solutions that respect all stakeholders, improve our common understanding and establish sustainable mutual trust

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A EURORDIS RARE DISEASE DAY® EVENT

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Proceedings

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1. The Symposium

Rapidly-advancing science and technology now create growing opportunities to develop more innovative medicines than ever before. Nonetheless, the rare disease community is still facing problems accessing these medicines in Europe.

The goal of the 2nd EURORDIS Multi-Stakeholder Symposium in February 2017 was to bring together stakeholders playing a key role in getting medicines and therapies to rare disease patients, and to initiate a dialogue and cooperative process that respects the interests of all stakeholders and that will ultimately lead to solutions for improving patients' access to rare disease therapies[1].

The 2017 Symposium brought together nearly 400 participants including patient advocates, academics, clinicians, policymakers, regulators, investors, members of the EURORDIS Round Table of Companies and other representatives from the healthcare industry, as well as from payers and health-technology-assessment authorities.

EURORDIS released a work-in-progress reflection paper ahead of the Symposium entitled 'Breaking the Access Deadlock to Leave No One Behind'. The paper offered a synthesis of EURORDIS' analysis, reflections and perspectives on the issue of access to medicines for people living with a rare disease. It expressed a set of possibilities rather than a position and is open to discussion.

This edition, which built on the 1st EURORDIS Multi-Stakeholder Symposium held in February 2016, culminated with the intention to form of a new multi-stakeholder group that will draft a 'One-Text', i.e. a Plan of Action for all stakeholders to collaborate on improving patients' access to medicines. This process will aim to enhance and sustain trust between the various stakeholder groups, a fundamental condition to achieving this ultimate goal.

[1] To view the morning plenary of the 2nd Multi-Stakeholder Symposium, visit here. To view Symposium documents go to: http://www.eurordis.org/symposiumdocs

2. The method for collaboration

The 2017 Multi-Stakeholder Symposium relied on a specific approach to negotiation which was presented by Mr. Charles Barker at the beginning of the meeting.

The One-Text Process is a way in which negotiators and mediators manage complex subjects with numerous stakeholders who hold conflicting views and exercise very different levels of authority[2].

The One-Text process relies on the Seven Elements:

For the collaborative process to work, the initial step must always involve the understanding and clarification of interests: what are the hopes, aspirations and fears of each stakeholder group? After this, it is important to come up with as many options as possible whilst looking for the optimal way forward and keeping the notion of fairness and legitimacy in mind.

The 2nd Multi-stakeholder Symposium was therefore the initial step in this type of process, setting the foundations for collaboration and negotiation based on the One-Text. This

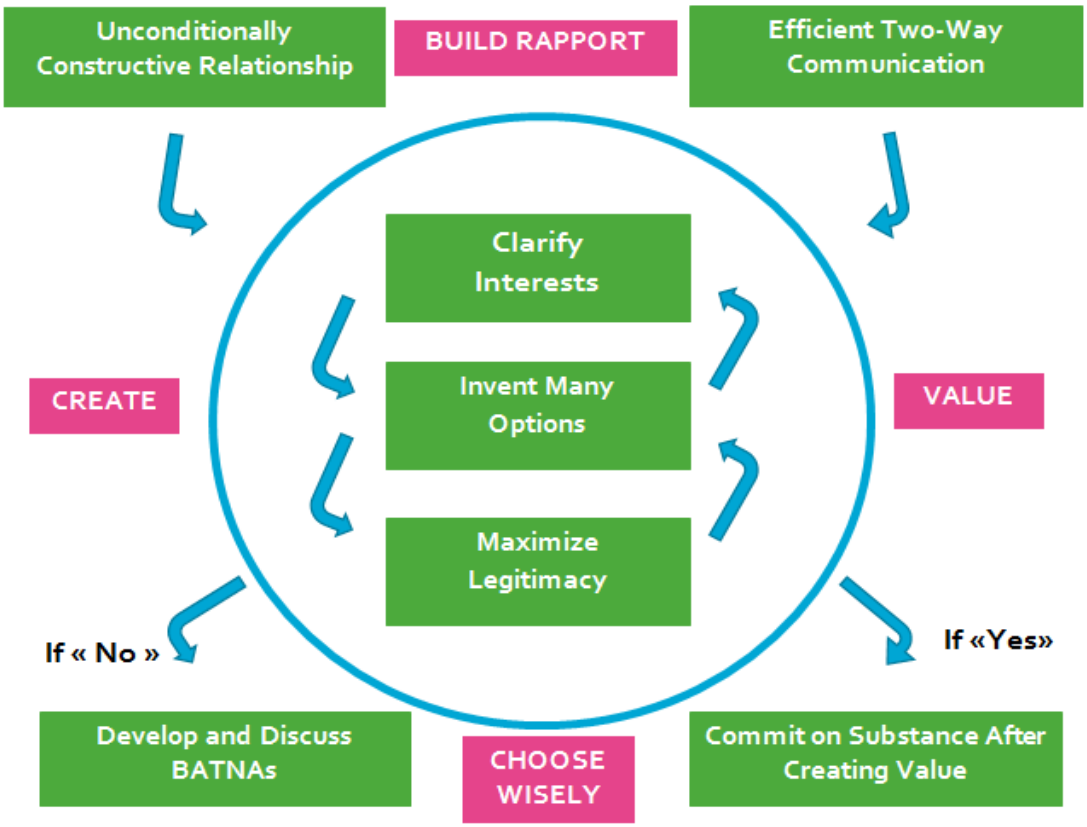
[2] © PrimeMover Associates, Inc. 2017. All rights Reserved
Both the *One-text Process* and the *Seven Elements* are concepts created by PrimeMover Associates. PrimeMover Associates is an international collaboration and conflict management firm providing training, advice, mentoring, and mediation services to business, government, non-profit, religious, and civil society organizations in health care, financial services, technology, communication, energy, diplomatic, education and manufacturing sectors. For further information please contact Charles Barker, Managing Director at +1 847 644 2494 or cb@primemover.ch. www.primemover.ch; www.cmiconcord.com.

single negotiating text involves clear guidelines with: a facilitator, a set of drafters from each stakeholder group taking a more neutral and collaborative position, as well as a group of commentators that will review the different versions of the draft until a 'yes/no' choice end-point is reached. Beyond the group of commentators, broader public consultations will be organised to collect additional views.

The designated drafters will aim to manage efficient communication among stakeholders and to protect stakeholder working relationships. The process helps these participants avoid positional thinking that sub-optimises results and that can even paralyse talks by intransigence over mutually incompatible demands. Instead, it helps them build the mutual understanding, emotional balance, respect, trust, openness to persuasion, and creativity that complex solutions such as improving access to rare disease therapies require.

The designated committee of drafters will take a collaborative approach to negotiation[3]:

Collaborative Negotiation Congruent Seven-Element Strategy



Source: Adapted from Barker, C. (2017) Prime Mover Associates

With the ideas and options discussed during the 2017 Multi-Stakeholder Symposium, the committee will draft a first version of the 'One-Text'. This first draft may include many different options for various parts of the problem, including multiple, mutually inconsistent

[3] For a good overview of the characteristics of a collaborative negotiation style versus those of a positional style, see: http://bit.ly/2olgJi1

options to address the same aspect of the overall problem[4].They will then present it to the group of commentators with the question *'what is wrong with this?'*, they will collect the criticism and re-draft a second version to be submitted for consultation once again. In this process, drafters need to be careful to avoid soliciting proposals for new options or to encourage positional thinking because commentators *will* expect their suggestions to be added in the next draft. They rather need to clarify positions and consider the rationale and not the proposal itself.

The cycle of drafting is repeated until it is felt the draft cannot be improved any further. At this stage, the text is presented to the stakeholders as a 'yes/no' choice. The goal is a sufficiently broad agreement to take effective action. This does not necessarily mean unanimity as a majority, or even a plurality, of stakeholders may be sufficient to take meaningful action towards resolving a problem. Ideally, a final draft should be presented at a future third Symposium, to be held in February 2019. In between, it is our aim for a successful process, to hold also high level meetings to gather further input, alongside more technical meetings to contribute to the drafting of the 'One-Text'.

[4] Charles L. Barker (2017) 'Using the One-text process', PrimeMover Associates, available at: http://bit.ly/2op4hNF$ (This section is based on this document).

3. Setting the scene

In line with the collaborative approach outlined above, the first step is to ask stakeholders what interests of theirs are affected and to identify the priorities of each group. This was the aim of the morning plenary of the Multi-Stakeholder Symposium.

3.1. What are the interests of pharmaceutical companies developing treatments for rare disease patients?

During the first panel of the Symposium, as an essential step in putting the method of collaboration in gear, six representatives of the pharmaceutical industry exposed the interest of their organisations to start the conversation on a 'level playing field'. To synthesise, the interests of pharmaceutical companies developing treatment for rare disease patients include:

- **Predictability**. Incentives and protection of intellectual property (including market exclusivity) are considered necessary to ensure a safe, predictable environment for research and innovation to take place. Pharmaceutical companies also welcome mechanisms put in place to avoid abuses of the system and call for a reinforcement of these that would reinforce trust between stakeholders.

- **Price**. Although this cannot be solely defined based on production costs, it is a key piece of the equation to pursue further innovation and ensure returns on investment.

- **Keeping innovation moving forward.** Often the science is there but it is blocked by cost issues and administrative hurdles.

- **Creating value for patients**. Incorporating patient preferences and increasing awareness of patients' essential needs are imperative for better decision-making. In this sense, incentives need to be associated with value creation.

- **Partnering with patient groups.** Considering the need for patients' input into the medicines development process, pharmaceutical companies are open to partnering with patient groups that can facilitate access to this pool of knowledge.

- **Innovative reimbursement and regulatory solutions.** Pharmaceutical companies are open to new forms of negotiation as long as the predictability of their markets is maintained.

- **Better education of both investors and the public.** Very often, pharmaceutical companies are perceived as a 'normal' industry when in fact it is developing 'life-saving' therapies. On the one hand, investors focus on how well their stock performs and on the other, the public sees them as greedy multinationals. Better awareness of the interests of pharma is needed.

3.2 What are the interests of payer and HTA bodies when considering how to improve access to rare disease therapies?

The second panel of the Symposium aimed at understanding the interests of the stakeholder group sitting at the other side of the negotiation table: the payers and HTA bodies. Five representatives of this stakeholder group exposed their interest as the following:

- **Robust evidence of medical benefit.** It is often the case that HTA bodies and payers receive a high number of orphan medicinal product applications but it is impossible for them to quantify the additional benefits of all of them due to a lack of robust evidence. HTA bodies and payers need proof of effectiveness for approval of medicines.

- **Early dialogue between the industry and the payer/HTA body.** Often, clinical trials are designed to measure particular endpoints that may not consistently correspond to the gaps in data that HTA bodies and payers are looking for. Calling for EMA scientific advice or payer involvement earlier on could fill in these gaps.

- **Patient engagement.** Related to the issue of evidence generation, payers and HTA bodies welcome a structured and systematic patient involvement. Their participation is very valuable in defining the outcomes and criteria that should determine the approval of a therapy as they are experts in their diseases and on the response to therapies.

- **More visibility on price-setting.** Payers are often concerned by the uncertainty of whether prices of medicines truly reflect the cost of investment and the added medicinal benefit. This is principally due to budgetary and sustainability issues of the healthcare system and the health & safety of patients. Payers most often engage in price negotiations in a reactive way, as the price seems to already have been decided. Payers would welcome an earlier involvement on price-setting and a higher degree of visibility of the factors justifying the price of medicinal products.

- **Meeting high unmet medical need.** Even if the question of early-access is fairly controversial, payers and HTA bodies are committed to meeting high unmet medical need and open to engage in initiatives like Adaptive Pathways which allow for accelerated development of medicines. What payers and HTA bodies want is for post-conditional authorisation data to be collected to fill in evidence gaps. One such solution would be through the creation of registries gathering comparative data on patient-relevant endpoints. ERNs offer a great opportunity in this respect.

3.3 Success factors for collaboration in relation to access to therapies

3.3.1 Existing initiatives

A number of existing initiatives or pilot projects were presented during the afternoon plenary of the first day of the Symposium. The aim of this was to provide some pointers as to what successful collaboration in relation to access to rare disease therapies could look like and identify 'best practices'. These included:

> **European Medicines Agency's PRIME and Adaptive Pathways:**
>
> o Priority Medicines (PRIME) enables accelerated assessment and timely access to treatments which is a value in itself. It reinforces scientific (parallel HTA) advice and regulatory advice leading to an increased likelihood of robust and useful data generation. Another expected benefit is that PRIME could steer medicines R&D towards unmet medical needs.
>
> o Adaptive Pathways (AP) addresses the 'access vs evidence' conundrum. AP aims at reducing uncertainties and at enabling the development of non-conventional products (i.e. gene therapy). As randomised clinical trials are complemented with other methods for evidence generation, the tool box for evidence generation is enlarged. AP introduces more flexibility into the system and leverages multi-stakeholder collaboration.

> **Engagement of patients in small population clinical trial design:** Patients should be listened to when developing clinical trials in small populations considering the training of patients in clinical trial design and the immense pool of knowledge they have as experts in their own condition.

> **EUnetHTA:** The aim of this 3rd Joint Action on HTA is to have production of joint assessments to be used at national level. A key component would be the inclusion of patient engagement in early dialogues in parallel to HTA scientific advice.

> **Mechanisms of Coordinated Access to Orphan Medicinal Products (MoCA):** This is a multi-stakeholder collaboration initiative in which companies get advice from payers around data requirements for reimbursement decisions, patients are able to express their perspective, while for payers it represents a horizon-scanning opportunity and the chance to affect how the company will gather evidence. Final recommendations are non-binding. There are however a number of challenges with this initiative including the lack of a single payer voice, the lack of a common mandate for payers (legal, political and organisational), independence concerns on the part of payers (i.e. will they be biased by MoCA when doing the real assessment?) and a lack of consensus between payers and regulators on early collaboration.

3.3.2 Success factors

The strong points of these existing initiatives and other sorts of activities that should be maintained or further explored were also discussed in the last session of the first day of the Symposium. These included:

- **Maintaining the urgency to have new products approved** as key interest to all stakeholders. This is the starting point to find a common ground for collaboration.

- **Patient involvement in early dialogue** is supported in initiatives like EUnetHTA. In the future, this will help reduce the uncertainties at the time of reimbursement.

- **Creating patient-safe harbours,** as MoCA's three-way dialogue.

- The potential of **involving patients in decision-making within the healthcare system**. It was discussed that it is necessary to put patients in the 'cockpit' with patient-based data as a compulsory criteria and creation of a system where collecting this patient data is the norm.

- **Providing training and support for patient engagement**. Patient participation should be more than just sitting around a negotiation table. In some countries like in Belgium, decisions on reimbursement are being discussed with patient organisations and patients/citizens perspectives are taken on board. Umbrella patient organisations play an essential role in this respect.

- **Multi-criteria decision analysis (MCDA),** which is being progressively used. This involves the consideration of several criteria, other than cost and efficacy, in reimbursement decisions for orphan drugs. MCDAs provide a structured framework for the comparison of these multiple options (or criteria) relating to a drug or a disease.

- **Common HTA methodology across EU.** There is a very high potential with these initiatives, in fields like horizon-scanning which allow for economies of scale in avoiding duplication and the waste of precious resources; or in sharing information and eventually engaging in common HTA assessment and joint negotiation.

- Moving **from value-based pricing to value-informed pricing** that evolves with adaptive evidence, thus reducing uncertainties and increasing the willingness to pay for orphan therapies.

4. Three themes for improving patient access to rare disease therapies

After eliciting the interests of both groups during day one, there was general consensus that a collaborative approach taking into account these interests was necessary to improve access to therapies. However, it still remained open how to breach existing barriers and whether it would be possible to bridge all interests. After a negotiation simulation during the final plenary, it became clear that applying the principles of collaboration presented at the start of the day is extremely challenging in practice.

Therefore, the second day focused on exploring in more depth *how* collaboration can be achieved. The structure of the Symposium was divided in six breakout sessions along three broad themes: Quality Data Generation; Value for money across Europe; and Outcomes. During these sessions, initiatives that have already been pilot-tested or at least conceptualised were discussed. In each session both challenges and opportunities of each initiative were explored.

4.1. Quality Data Generation

The morning breakout session (1) focused on registries as an option for improving access to rare disease therapies. The afternoon breakout session (4), introduced a new option that could enable quality data generation: European Reference Networks.

4.1.1. Breakout Session 1: Pan-European disease & product registries to address needs of all stakeholders

Patient registries could be simply defined as *infrastructures* that store patient information into a database. The role that a registry may play in drug development and access may be different. Time is the element that exerts an important impact on registries, making them evolve as new stakeholders/partners with different needs and expectations engage and potential new uses emerge. Funding can also fluctuate over time and the underlying technology sustaining registries can get rapidly outdated. Interoperability between databases is another factor to maximise registry data exploitation and it is currently being explored by ongoing EU-funded initiatives.

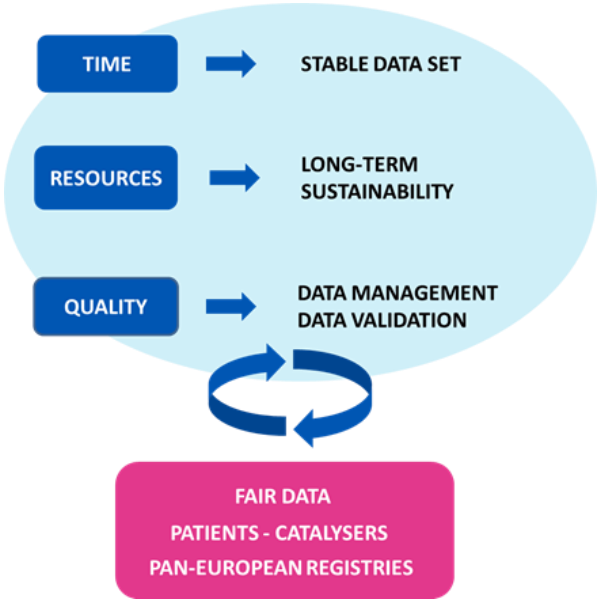
4.1.1.1. Challenges

- Setting up a registry takes **time** and requires a collaborative effort from all stakeholders involved to clearly identify the data needs and expectations from each stakeholder group. For instance, natural history studies require a minimum of 5 years of stable data.
- **Expert data management** is essential to obtain **high-quality data** and therefore training to data-entry users (patients, among others) is necessary to ensure the homogeneity of the data.

- **Interoperability** between different data sources is not fully resolved at present.
- Other issues such as **data validation** and validation methods need to be taken into account if registries are going to be used to provide data at the level of HTA and reimbursement.
- Ensuring the **long-term sustainability** of the registry is one of the main challenges, particularly in terms of funding.

4.1.1.2. Opportunities

- **Patients and patient groups** should act as **catalysers** to build trust and bring together researchers and clinicians. Patients also play an important role in data-entry to keep it constantly updated which is key to reflect disease progression. From this data, information on natural history of the disease and effectiveness of treatments can be extracted. Within registries, patients should be part of the governance and advisory board and be instrumental on applying the dynamic informed consent.
- Data need to be **Findable, Accessible, Interoperable and Reusable** according to the FAIR principles in order to turn non-structured data sets into compatible data. This is because high-quality data is not only of high-quality due to its content but also because of the ability of this data to be shared.
- **Training of patients and professionals on FAIR data-entry.** To ensure that data in registries complies with the FAIR principles, those inputting data need to receive the tools to do this. Initiatives like the International Summer School on Rare Disease and Orphan Drug Registries or the RD-Connect Bring Your Own Data Workshops exists, but continuous funding for them is needed.
- **Cooperation at EU and international level,** development of common guidelines and data standardisation would help the use of data across borders. In rare diseases, pan-European rather than national registries should be pursued.



4.1.2. Breakout Session 4: How European Reference Networks (ERNs) could become the solution/enablers of quality data generation?

European Reference Networks will virtually connect centres providing highly specialised healthcare in rare and complex medical areas where both patients and disease knowledge are scarce. There are currently 24 approved ERNs with inclusive and comprehensive disease coverage, involving 370 hospitals and 1,000 highly-specialised medical units in 26 countries. ERNs will help build the expertise to diagnose and manage patients through support to health care professionals within a formal networking structure. For patients, ERNs mean having access to the best specialists, with the expertise travelling rather than the patient, thus reducing inequalities in healthcare across the EU. ERNs will have a multi-disciplinary approach and will test innovative care models. The evidence generated will be the basis to produce better clinical practice guidelines. ERNs have the potential to also contribute to research through large multinational clinical studies.

4.1.2.1. Challenges

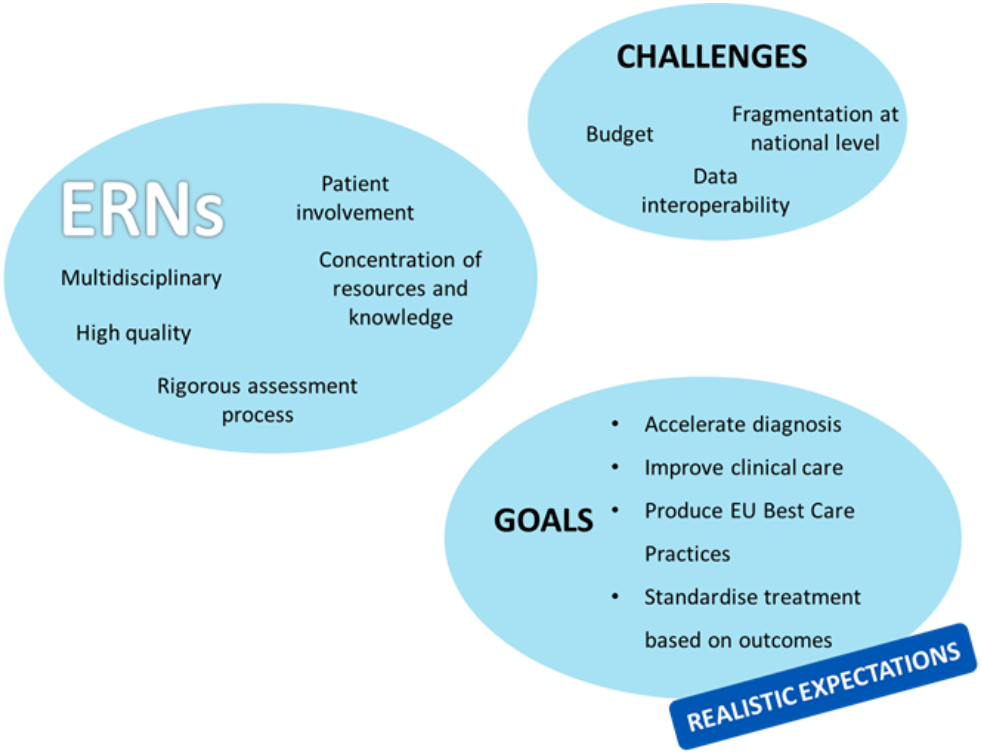
- **Time**, as it will take years for ERNs to reach their full potential. For instance, registries need time for stable data collection (around 5-10 years)
- ERNs have been assigned a **low budget** that may need to be reconsidered in order to ensure their long-term sustainability. Currently ERNs are assigned about 20,000 € per year for coordination activities.
- **Fragmentation** in standards of care, research and registries at national level that needs to be overcome for ERNs to be fully operative.
- **Avoiding duplication of efforts**. Abundance of existing registries and databases should be explored and adapted.
- **Data interoperability** among registries may not yet be resolved.
- **Ownership/custodianship** of the data needs to be clarified.
- **Legal framework** for data-sharing as well as for the practice of clinical trials must be put in place.

4.1.2.2. Opportunities

- ERNs offer the possibility of improving the knowledge on the natural history of diseases and therefore of **reducing time to diagnosis**. Clearly defining the natural history will also help to identify the best clinical outcome measures and standardise treatments based on these outcomes. Natural history studies will also be important to measure success of ERNs in terms of added clinical value and improving patient care, as access to drug therapy does not apply to every disease.
- ERNs will have **an inherent mark of 'quality'**, as networks and health-care providers have each been through a rigorous assessment process and have had to

demonstrate that they meet certain core criteria. Therefore, it is anticipated that ERNs will be viewed by the field at large as a beacon of excellence and expertise.

- **Patients and patient organisations** are central in partnering with clinicians to raise awareness at national level about the benefits that ERNs can provide. From a patient perspective, ERNs can help the **building of trust** and relationships through collaborations and so provide the data that matters to patients.
- **Real expectations** need to be set up for the first 5 years in terms of collaboration among the centres/networks, data sharing and creation of registries to ensure commitment and not lose the momentum. Adaptation and flexibility are key.
- **EU-wide registries** are essential for rare diseases as patients are scattered across the continent.
- Important to find a mutually beneficial and ethically sound way for ERNs to **engage with industry** to optimise opportunities on both sides while considering conflicts of interest. Multi-stakeholder disease registries would help to generate post-authorisation data and contribute to therapies getting quicker to the patient.



4.2. Value for money across Europe

The morning breakout session (2) focused on an emerging option proposed by the European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-VAL) on 9 principles. The afternoon breakout session (5), explored an option that has implications for rare diseases: Proposals for coordination of HTA across Europe.

4.2.1. Breakout Session 2: Towards a common European value and funding system for orphan medicinal products: implementing the ORPH-VAL principles

The Recommendations from the European Working Group for Value Assessment and Funding Processes in Rare Diseases (ORPH-VAL) were presented and the discussion focused on the alignment of different countries with this consensus document. Value (i.e. relative worth, merit or importance: how much are we willing to pay?) vs value for money (is it worth its price?) were differentiated. The value of orphan medicinal products (OMPs) can be measured at different levels: 1) patient level (survival, life expectancy, morbidity, quality of life, patient economic burden, existing treatment options, side effects and convenience); 2) healthcare system level (resources and budget, healthcare system organisation) and 3) societal level (family/carer quality of life, family/carer economic burden and societal economic burden).

The document drafted by ORPH-VAL proposes 9 principles to help improve the consistency of OMP pricing and reimbursement assessments, while taking into consideration the characteristics of rare diseases (rarity, level of uncertainty):

Principles on OMP decision criteria

1. **OMP assessment should consider all relevant elements of product value in an appropriate multi-dimensional framework.** Some core elements should be common to all countries, but there may be elements that are differently prioritised across countries.
2. **Pricing and reimbursement decisions should be founded on the assessment of OMP value and adjusted to reflect other considerations beyond product value.** Informed value: the price should in part be informed by magnitude of product value in light of price-value precedents for other medicines (benchmark). Societal preferences, rarity, affordability and sustainability of innovation in rare diseases should also be considered. Incremental cost-effectiveness ratio thresholds (ICER) should be modulated to reflect specificities of rare diseases and the need to maintain innovation.

OMP decision process

3. **Those making P&R decisions about OMPs at a national level should take account of all official regulatory and HTA work on OMPs undertaken at European level.** Avoiding duplication at national level: make use of the evidence already existing at EU level.
4. **Assessment should incorporate the expertise and perspectives of both healthcare professionals and patients.**

	5. **To accommodate uncertainty, value assessment and P&R decisions should be adaptive subject to the need and availability of information over time.** It must be clear from the start what type of information will be needed and what will be the consequences if this is not met. Data gathering should be collaborative. 6. **Consider all eligible patients within the authorised label of an OMP in national P&R decisions.** Different decisions on access may then apply to different sub-populations.
OMP sustainable funding systems	7. **Funding should be provided at national level**. This is to avoid inconsistencies and inequalities in regional access. 8. **Evidence-based funding mechanisms should be developed to guarantee long-term sustainability.**
OMP EU coordination	9. **In the future there should be greater coordination of OMP value assessment processes at European level.**

4.2.1.1. Challenges

- **Valid evidence for OMP assessment.** As a general rule orphan medicines have to be recognised as having additional benefit. This poses difficulties in collecting "perfect" evidence for rare diseases as the same level of certainty is expected as with other medicines.
- **Differences between and within countries.** It is often problematic to have common assessment across countries because of the different levels of national and regional GDP and also the differences in societal preferences.
- **Differences in the level of patient engagement.** For example, while the UK has significant involvement of patients in a very structured manner, the level of involvement of patients in Germany and France is not documented.

4.2.1.2. Opportunities

- Having a **broader definition of value** was seen as positive by countries like Germany and France where orphan medicinal product assessment still follows a two-step process. This would be helpful when considering the difficulties that exist in collecting evidence for orphan medicinal products.
- Having a **common base of relevant elements of product value,** but allowing countries to **prioritise** them differently, could be an incentive for closer collaboration across borders.
- The addition of more **structured patient involvement** into the process ensures real-world experience of a rare disease allowing the identification of relevant outcomes and what level of improvement is clinically meaningful.
- For the UK, which already has a separate assessment for orphan drugs, having more **flexible incremental cost-effectiveness ratio thresholds** reflecting specificities of the diseases and drugs could be considered.

4.2.2. Breakout Session 5: Proposals for coordination of HTA across Europe: implications for rare diseases

In the European Union, while risks, benefits and efficacy are assessed at the level of the European Medicines Agency, national and regional HTA bodies are in charge of looking at the relative effectiveness of the therapy, before pricing and reimbursement are negotiated with payers. In terms of HTA, each country has its own way of evaluating. For instance, only NICE (UK) accepts real-life evidence coming from registries. This creates differences in access across Europe. Therefore, there is a need for HTA bodies to agree on and have common sources of information. The objective of the EUnetHTA Joint Action 3 (2016-2020) is to define and implement a sustainable EU cooperation on HTA. Currently, 80 partners (national, regional and non-profit agencies) produce or contribute to EUnetHTA. There are two arms of cooperation: scientific and technical; and strategic between Member States, supported by the European Commission.

In October 2016 – January 2017, the European Commission held a consultation to evaluate the level of engagement preferred. Five options were opened to consultation:

Key characteristics	Option 1 The status quo –voluntary cooperation on HTA (until 2020)	Option 2 Long term voluntary cooperation on HTA (beyond 2020)	Option 3 Cooperation on collection, sharing and use of common tools and data	Option 4 Cooperation on the production of joint REA reports	Option 5 Cooperation on the production of joint full HTA reports
Regulatory	Non-legislative	Non-legislative	Legislative	Legislative	Legislative
Participation of HTA bodies and industry	Voluntary	Voluntary	Compulsory (tools) Voluntary (HTA)	Compulsory (tools) Voluntary / compulsory (HTA)	Compulsory (tools) Voluntary / compulsory (HTA)
Uptake joint output	Voluntary	Voluntary	Compulsory for tools	Compulsory for tools and REA	Compulsory
Financing	Largely depending on EU budget	Largely depending on EU budget	Mixed funding model (EU budget + MS + industry contribution)	Mixed funding model (EU budget + MS + industry contribution)	Mixed funding model (EU budget + MS + industry contribution)
	Ending 2020	Long-term	Long-term	Long-term	Long-term
Main joint output					
a. Common Tools/templates	(✓)	(✓)	✓	✓	✓
b. Joint REA	(✓)	(✓)	(✓)	✓	✓
c. Joint Full HTA	(✓)	(✓)	(✓)	(✓)	✓
d. Early Dialogue	(✓)	(✓)	✓	✓	✓

(✓): partial delivery

✓: complete delivery

Source: Inception Impact Assessment for an EU initiative for strengthening EU cooperation on Health Technology Assessment (HTA)Search for available translations of the preceding link

While no one in the Symposium openly backed options 1 & 2 demonstrating a common will towards stronger cooperation, the fact that no consensus was found between options 3, 4 and 5 is a sign that a number of challenges still remain.

4.2.2.1. Challenges

- **Low uptake**. National uptake is the general implementation of any EUnetHTA output in a national context and may include the usage and implementation of the EUnetHTA tools and Joint Assessments. While a number of countries (e.g. Austria and Spain) use a high number of tools created by EUnetHTA, the general uptake remains relatively low.
- **Fragmentation**. There are very important differences in procedural framework and in methodologies in EU countries. This makes option 5 very difficult to achieve. However, it is important to ensure that the right level of cooperation is achieved so that the project does not add another layer of complexity and reaches its goal of avoiding duplication. In addition, higher agreement between national HTA bodies would be beneficial to the industry which often struggles to devise an evidence generation plan that fits all national frameworks.
- **Sustainability.** One of the main problems of EUnetHTA is the lack of funding post-2020. There is no guarantee that the European Commission will continue funding Joint Actions. The option of funding cooperation through industry fees has ethical and conflict of interest implications. It is important to keep the independence of HTA bodies.

4.2.2.2. Opportunities

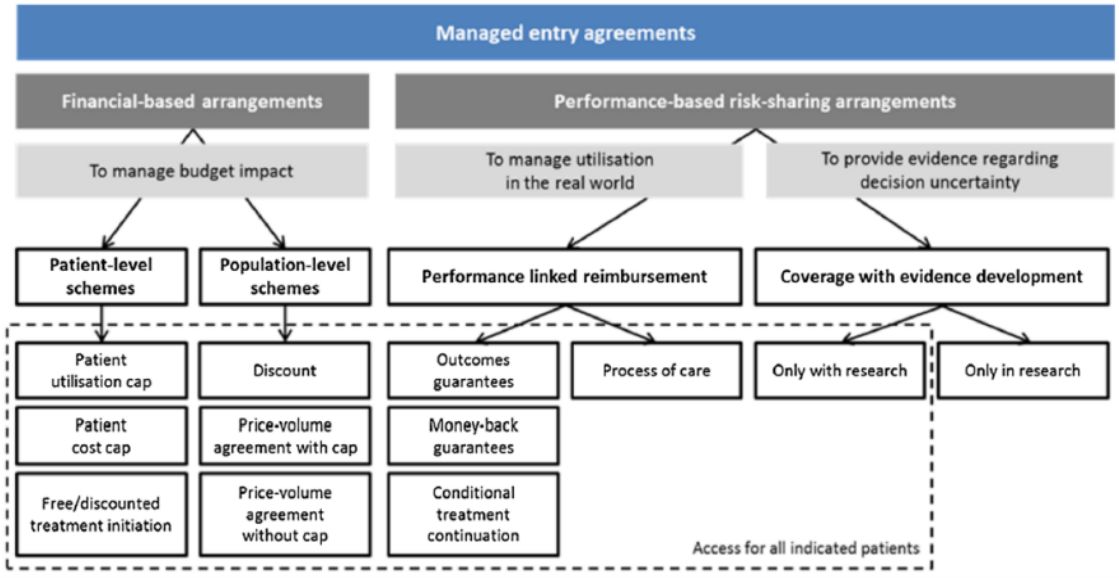
- **Will and building of trust.** One of the main achievements of the project has been the building of trust between national bodies. HTA Joint Actions have been going for a period of more than 10 years and the commitment and will to strengthen the collaboration is getting stronger. For sustainability, the EC is exploring a fee-for-service scheme.
- **Structured patient engagement.** The structured input from patients which are relevant to the specific questions asked for HTA is particularly important in the case of rare diseases where patients for each disease are scarce and scattered. There is a need for patient training which is sustainable and standardised so that patients can be ready and know when their voice can be heard. Collaboration between organisations like HTAi and EPF can make a difference.
- **Early and continuous dialogue on evidence**. A stable mechanism that sets what an acceptable level of evidence across Member States, particularly for rare diseases, would guarantee that patients across Europe get the same level of access to therapies.
- **Avoiding duplication and scaling up evidence**. Listed as one of the main achievements of EUnetHTA was the development of joint pools of evidence. For rare diseases it is particularly important to put the scarce high-quality evidence together and use it at coordinated EU level.

4.3. Outcomes

The morning breakout session (3) focused on an emerging option: innovative performance based outcome agreements. The afternoon breakout session (6) explored the potential for European collaboration among payers and companies.

4.3.1. Breakout Session 3: Innovative performance based outcome agreements

This breakout session discussed Managed Entry Agreements (MEA) as a form of innovative performance based outcome agreements. The MEA is an agreement between the manufacturer and the payer with the objective to facilitate access of an innovative product onto the market under specific conditions to circumscribe uncertainty surrounding a novel product, obtain best value for money and ensure affordability. Each stakeholder group agrees upon a certain degree of risk sharing and specific engagements to further assess the added-value of the new product. There exist different forms of MEAs, including financial-based agreements and performance-based agreements.



MEAs are typically classified into finance based agreement and outcome based agreement

Source: Garrison (2013)

CRA Charles River Associates

4.3.1.1. Challenges

- **Defining patient-relevant outcomes.** One of the most challenging tasks is actually deciding the kind of data that needs to be collected, the outcomes that need to be measured and how this is going to be done in a way that is relevant to the patient. For instance, would it be patient-reported outcomes or measures of the quality of life?
- **Choosing surrogate end-points.** This is critical in small populations like those of rare diseases. A surrogate endpoint of a clinical trial is a laboratory measurement or

a physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions or survives. Changes induced by a therapy on a surrogate endpoint are expected to reflect changes in a clinically meaningful endpoint.

- **Timing**. Selecting the timeline of an MEA is one of the most challenges steps and often a stumbling block in negotiations between the manufacturer and the payer.
- **Data collection and sharing**. Firstly, issues of data capture (like resource investment for this), of data quality and validation, and of dataset interoperability can obstruct the establishment of MEAs. In addition, the issue of data protection and privacy is a particularly delicate one. In the case of rare disease patients, sharing data to scale it up is very important for frameworks to function and so it is important to have a clear informed consent for the use of data.
- **Ethical balance**. Related to the issue of data mentioned above, it is important to ensure the right ethical balance between continuing to collect patient data to demonstrate the agreed upon outcomes and the burden and disturbance it places on rare disease patients' lives.

4.3.1.2. Opportunities

- **Openness and trust-building.** Whilst there is a tendency towards rigid and objective guidelines, it becomes more and more clear that rare diseases demand adaptability and subjectivity. Those participating in MEAs are open and build a trusting relationship that allows for this flexibility. Early and broad discussions are essential to ensure that adaptability is achieved and maintained.
- **Patient engagement.** As it has been demonstrated in many other emerging options, the inclusion of patients is the way to achieve a process that truly responds to their needs and is sustainable. Interviewing clinical trial patients was discussed as an opportunity for MEAs. In particular, involving patients in assessing which outcome to report on, like for instance, an objective outcome (walking) versus a subjective outcome (feeling energised).
- **Data custodianship.** In the field of rare diseases it is of great interest that data is shared but rather than talking of data ownership one proposed option is to shift to data custodianship. Clearly defining who will be entrusted with the custody of such data is essential and exploring alternative data collection methods that aim to minimise patients' lives too.
- **Explore the role of ERNs and EUnetHTA.** Combining the opportunities offered by various initiatives into an integrated system can have a great positive impact on access to rare disease therapies.

4.3.2. Breakout Session 6: Potential for European collaboration among payers and companies

Access to medicines has become an increasingly polarised discussion over the years with rare diseases becoming the preferred exemplary case of these tensions. The principal conflict is pictured to be between companies and payers. The aim of this session was to explore whether both groups have the same vision of these tensions and to look at the opportunities that are open for collaboration between them in Europe.

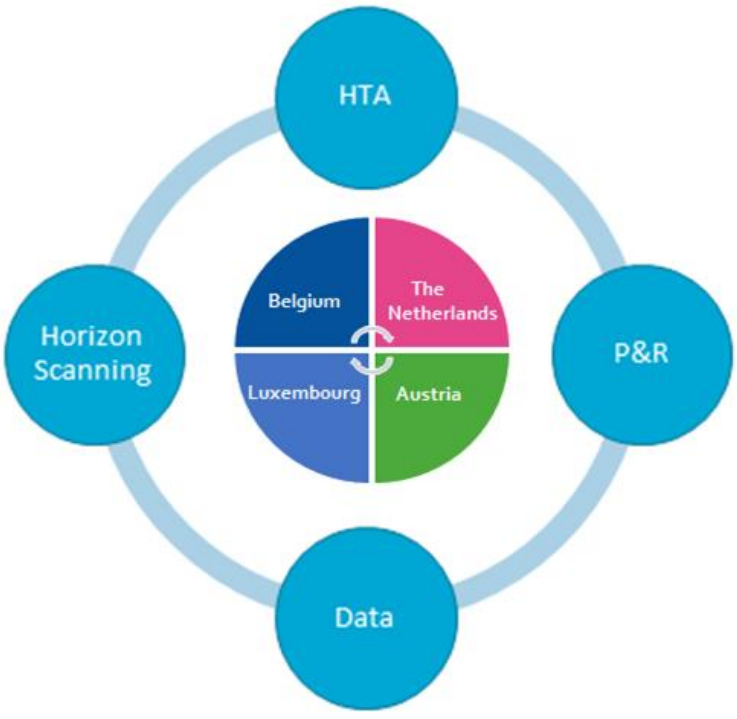
The main focus of the discussion turned towards the commonly called 'BeneluxA' initiative that is pioneering collaboration and is a tangible, in-progress project:

The BeneluxA initiative

In 2015, Belgium, Luxembourg and The Netherlands began joint negotiations with pharmaceutical companies, enlarging their negotiation power and moderating the price of orphan drugs. In June 2016, Austria also joined this initiative.
Although this pilot project is sometimes perceived as solely a price-cutting exercise, it in fact goes beyond joint negotiations with pharmaceutical companies. The four countries cooperate on four different taskforce domains: HTA; horizon scanning; data exchange; and pricing and reimbursement.

The main goal is to accelerate access to patients and avoid unnecessary duplication. The advantage for companies is that they only have to submit one dossier and they directly have access to a larger patient population.

Collaboration is already in practice in all four domains. In terms of payers-pharma relations, when the pilot project started in 2015, the countries had to contact companies themselves and promote the mechanism, but increasingly, companies are approaching the project on their own initiative. Their participation is voluntary.



Challenges of BeneluxA

- **National regulations.** Often national law can clash and so, even if a project lead is assigned some tasks, these cannot be done jointly and duplication may still happen.
- **Regionalisation.** In many countries decisions for P&R are made at the regional level so it becomes even harder to align all stakeholders.
- **Involvement of patients.** There was a general acknowledgment that there is still great room for improvement in the involvement of patients in the project.
- **Recreation of existing initiatives.** The question was raised on whether the collaboration on HTA could not better be left to the EUnetHTA, in existence since 2006.

Opportunities of BeneluxA

- **Trust-building.** By looking further than just price, a trusting mind-set is established, which is essential in the engagement among countries and between countries and the pharma industry.
- **Accelerated access to patients.** Whilst it is sometimes believed that collaboration can slow-down the process, in fact the sharing of information can allow for better and faster decisions on pricing and reimbursement.
- **Common ecosystem for companies.** At the moment, the business model of a company cannot be built around the ecosystem of a single country due to the fragmentation of the EU market. The BeneluxA project allows companies to deal with several countries at once.
- **A learning environment.** The BeneluxA project is a good opportunity to learn lessons on joint procurement. The project is being monitored and assessment reports will be published allowing for reflection on the way forward.

The rest of discussions during this session revealed many different views on the matter of collaboration between payers and companies without clear consensus. The point of convergence was on quick access being a 'win' from the patient and the industry perspective and the fact that for this a change of ecosystem is needed. There was however no agreement on what the basis and rules of this new ecosystem should be.

Collaboration between payers and industry: points of contention

The following issues were raised during the session without consensus:

- **Sustainability of health system.** Do we need a long-term view of the process?
- **The environment for pharma companies is more complex than it looks.** They have to deal with payers, enter into hospital tender exercises and discuss with individual pharmacies. How can the environment be transformed?
- **Agreeing on evidence gathering before seating at the P&R negotiation table.** Do we need to agree on an acceptable level of uncertainty?
- **Elucidating societal preferences.** Do we need to know how important it is to treat rare disease patients vs. other patients?
- **Not every country has the same ability to pay.** Do we need to manage expectations and realise some countries will have cheaper prices than others?
- **Transparency of pricing.** Will collaboration on this be fruitful or not?
- **Harmonising price.** Is this the way forward? Not for industry.
- **Incentives.** A highly polarised issue: should they be cut or not?
- **Price-cutting.** Should discussions start with this or earlier on?

5. Conclusions and opportunities

This section will summarise the main challenges and opportunities identified throughout the two days of the Symposium and the way forward to a multi-stakeholder approach that can generate sustainable, affordable and actionable improvements in patient access to rare disease therapies.

Challenges

- **Time:** different timelines of all stakeholders.
- Long-term **sustainability**: of health systems and of collaboration initiatives.
- Ensuring **high-quality and patient-relevant data**
- **Fragmentation:** in national/regional health and innovation policies and in standards of care and research
- **Duplication:** of processes and of collaboration initiatives
- Differences in **patient engagement:** from country to country and between initiatives
- **Low Member State uptake** in collaboration initiatives
- **Ethical balance:** in conflict of interests, data collection and data sharing
- Need of a **new ecosystem for payer-industry relations**

Opportunities

- **Patients and patient groups** can act as **catalysers of trust and collaborators**
- Training for patients and professionals on **FAIR (Findable, Accessible, Interoperable and Reusable) data-entry**
- **ERNs** offer an unprecedented chance to **reduce time to diagnosis**
- Creation of **Pan-European registries**
- Consolidating a **common base of elements of product value**
- **HTA collaboration** can avoid duplication and scale up evidence
- Exploring existing intiatives (i.e. ERNs & EUnetHTA) as part of **integrated system**
- Move forward with **public-private partnerships**

Rare diseases are not only about health, they are about equity. Increasingly, the EU has to prove how it can be useful for its citizens and the EU added-value in rare diseases is indisputable.

Xavier Prats-Monné
Director General of DG SANTE
European Commission
at the 2nd EURORDIS Multi-Stakeholder Symposium

It is clear by now that a multi-stakeholder approach is necessary to improve access to rare disease therapies. The issue calls for all the stakeholders to ally and come together if the hope of improving conditions is to be achieved. During the closing to the Symposium, the call for an approach **driven from the bottom-up** but **supported from the top-down** was issued by participants.

This approach requires 3 key elements:

- Mutual trust: both to take risks and to discuss cost and price.
- Will: from all stakeholders (political, private and public sector).
- Investment: in research, people and initiatives.

In addition, the current socio-political framework, in which notions of solidarity, universal health access and universal Sustainable Development Goals are bearing principles, needs to be utilised to make all stakeholders accountable and together, reach the goals of improved access to medicines for people living with a rare disease in Europe.

The first step driving the bottom-up approach will be the drafting of the One-text with a number of representatives of stakeholders as proxies. This process will be ongoing throughout 2017 and 2018.