Rare 2030

Deliverable 6.2: Brief Describing New Policy Opportunities

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Introduction

Consultations and teleconferences with the Rare 2030 Panel of Experts (PoE) across 2019, 2020 and into January 2021, have been of critical importance to deliver and shape the final project outputs.

This multidisciplinary body was established in April of 2019 and involved, at the end of December 2020, **200 stakeholders from 38 countries.** The members represent all the major stakeholder groups required for rare disease policymaking: patients and patient advocates; ERN coordinators and clinicians; researchers; policymakers; Industry; and topic specialists from beyond the rare disease field.
Several clusters of consultation activities were organised, through topic-related subgroups, as follows:

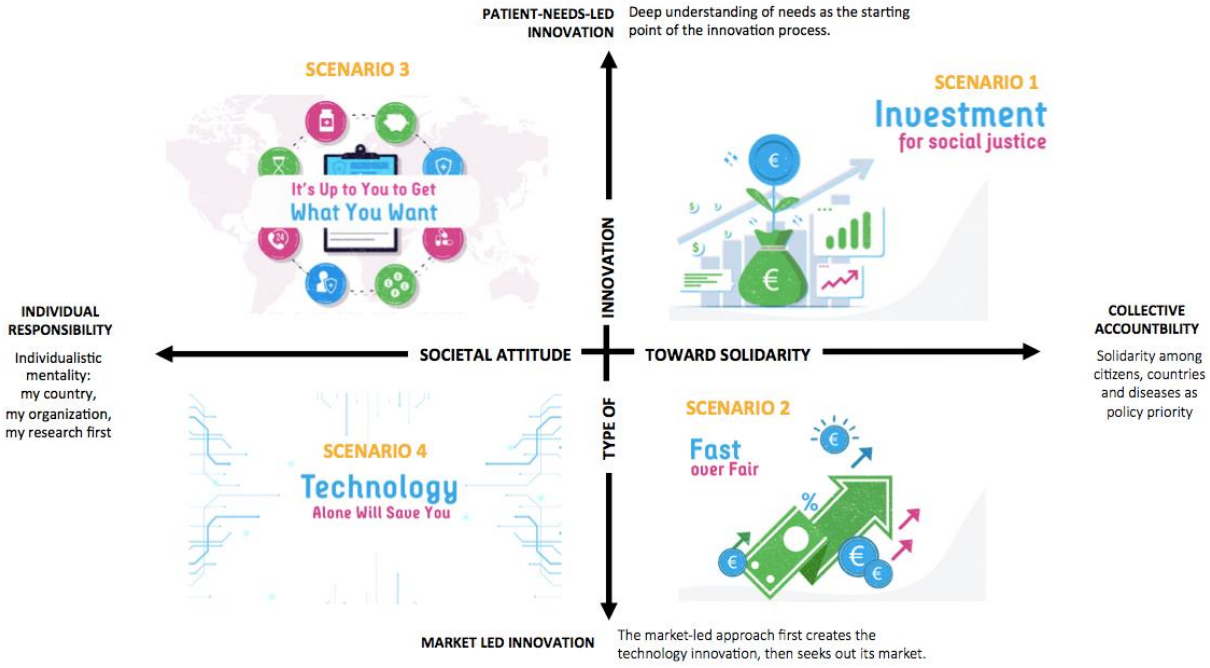
Sub-Group 1 – Political and strategic frameworks relevant to rare diseases
Sub-Group 2 – Data Collection and Utilisation
Sub-Group 3 – Accessibility and Availability of OMPs and Medical Devices
Sub-Group 4 – Basic, Clinical, Translational and Social Research
Sub-Group 5 – Diagnostics
Sub-Group 6 – Integrated Social and Holistic Care
Sub-Group 7 – Patient Partnerships
Sub-Group 8 – Access to Healthcare

Each cluster of PoE activity had distinct but interlinked aims:

- In May and June of 2019, the PoE members were asked to **review dedicated policy status quo documents**, namely the ***Knowledge Base Summaries***. In initial teleconferences of 2 hour slots, the PoE members were invited to share their responses to a number of key policy-oriented questions, which linked to the materials in the Knowledge Base Summaries. This exercise was intended to elicit expert views on the status quo, and, in particular, on successes of past policies for rare diseases. **The group was also asked, through these key policy questions, to identify remaining gaps requiring better application of existing policies, or the creation of entirely new policies and recommendations.**
- Following these initial calls, working documents were created by the UNEW team, one for each subgroup, **to comprehensively capture and cluster all of these comments** and policy-oriented suggestions on how to address identified gaps and advance each topic. These working documents were opened to the PoE members -in GoogleDocs format - for several weeks in the summer of 2019, for their continued elaboration and annotation, to provide comprehensive and extensive records of comments and counter-comments geared around those key questions. **Those debates**

represent crucial consultations with our myriad stakeholder groups, elucidating the issues which should be addressed in the project's final recommendations.

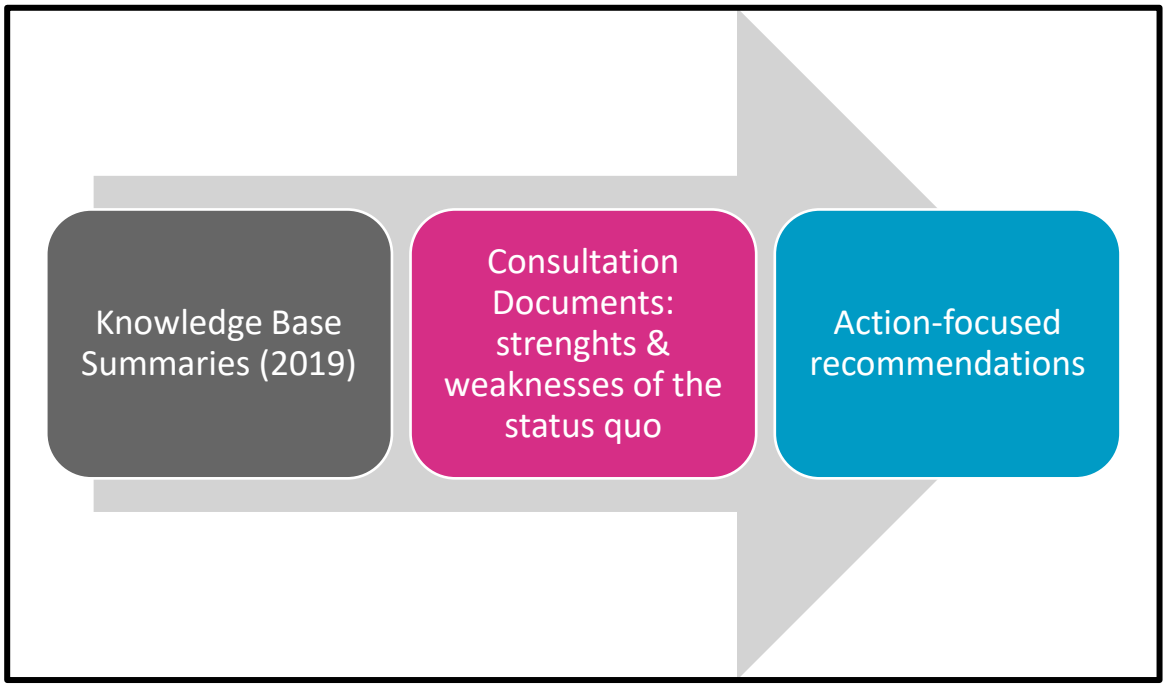
- In late summer and Autumn of 2019, the foresight study methodology progressed to consideration of past and -especially- future trends, ultimately enabling the creation of four contrasting future scenarios and extensive activities to identify the most preferable and plausible scenarios.
- In the Summer of 2020, focus moved to the back-casting phase. Here again, the inputs of the PoE were essential. Large teleconferences were organised once more, subgroup by subgroup. This time, the participants were asked to build upon their 2019 status quo assessments and identification of areas requiring new/revised policies, to actually generate tangible action-oriented recommendations. **They were asked to consider at all times the preferred scenario (Scenario 1, Investment for Social Justice)**



- The recommendations/action-focused comments identified across each of the 16 2-hour teleconferences in June of 2020 were further developed by the UNEW team, to produce a draft document presenting coherent recommendations for each of the 8 subgroups. These were circulated to the PoE, and feedback requested and obtained in January 2021.
- UNEW and EURORDIS combined the feedback from the PoE with comments and suggestions from a broad range of internal partner reviewers, across the period December 2020 – January 2021. This enabled the finalisation of chapters, one dedicated to each of the subgroup topics, which brought together a number of important Rare 2030 inputs. The resulting chapters include sections elucidating a 2030 vision; a goal; an overarching recommendation (suited for instance to a policymaker, to capture attention via headline messages); comments from young citizens; patient perspectives; and a section on how to measure success. The core of each chapter, however, is composed of the action-focused recommendations proposed by the PoE, designed to guide the RD community to the vision espoused.

For the purposes of this deliverable, therefore, a 'policy brief' for each of the 8 subgroup topics is defined as the combination of 3 distinct components:

- The **Knowledge Base Summaries**, which explain the status quo for the topic and highlights existing/past policies and recommendations, notable resources and initiatives, and trends emerging from a literature review: these documents were submitted for Deliverable 4.2 and can all be found here: https://www.rare2030.eu/knowledgebase/
- The **background consultative documents** generated from the PoE perspectives on the rare disease status quo and areas requiring new policies or renewed momentum. These are presented here as a series of **Annexes**.
- **The centrepieces of each of the 8 policy briefs are the sets of action-focused recommendations proposed by the PoE and elaborated into more coherent recommendations**, assigning a particular action to specific stakeholders. These recommendations for each topic are loosely subdivided into logical clusters (for instance, one cluster might be actions for European-level actors, with another set aimed at national authorities). **These sets of recommendations, finalised in the week commencing 25th January 2021, are presented below (pages 5-33) as the main body of these policy briefs**



The Three Components of the Rare 2030 Policy Briefs

Policy Recommendations for Topic 1: Political & Strategic Frameworks Relevant to Rare Diseases

At the European level:

- Greater pan-European - indeed sometimes global - collaboration is essential to address the health, research, economic, and holistic challenges posed by rare diseases, which know no borders and cannot be met by any single nation alone; in particular, the role of the European Union in the sphere of health should be augmented, through eventual adoption of a new charter
- A new Council Recommendation on an action in the field of rare diseases should be elaborated and adopted, as part of the new legislative and policy framework, following the overall assessment of the implementation of the current one, as demanded by the Council Conclusion of 16 June 2017 on Encouraging Member States-driven Voluntary Cooperation between Health Systems and the 2019 Special Report of the European Court of Auditors on implementation of Directive 2011/24/EU.
    - This new Council Recommendation should take into account specific recommendations pertaining to rare cancers (the rare diseases of oncology) set out in the Rare Cancer Agenda 2030 (JARC, 2016-2019)
- Application of the EU Open Method of Coordination to the rare disease field should be explored, along with the potential to add rare diseases to the agenda of the European Semester;
- Lessons must be learned from the COVID-19 pandemic, in terms of establishing the impact on already vulnerable rare disease populations and ensuring global, European, national, regional and local efforts to redress the damage and promote equality across all sectors, whilst capitalising on the positive momentum the crisis has created in terms of rapidly and efficiently streamlining procedures, research collaborations, clinical trials and regulatory activity.
- Consensus indicators should be developed at European level to monitor rare disease diagnostics, treatment, care, research, and holistic wellbeing, with countries encouraged to collect and pool such data to publically and transparently illuminate the status quo and enable benchmarking:
    - This could be achieved through the EU Open Method of Coordination and/or the Resource on the State of the Art of Rare Diseases Activities in Europe, and could build upon the EUCERD Recommendations on Core Indicators for National Plans and Strategies.
    - Such indicators should illuminate cross-country collaborations as well as national-level activities, and should serve the purpose of identifying good practices which might be expanded or replicated elsewhere
- To align the rare disease field with the growing trend for outcomes-based medicine, the incorporation of rare diseases (including rare cancers) to the 'State of Health in the EU' and to OECD activities concerning patient-centred outcomes, should be explored
- A dedicated multi-stakeholder body -with participation from all national competent authorities, along with ERN coordinators, patient advocates, Industry, researchers, and independent experts- should be established, with a remit to identify and assess best practices, and to review existing - and elaborate new - policies and recommendations on any subject under the 'rare diseases' remit.
    - This could be a new body, building on the new Rare Diseases Stakeholder Network under the EU Health Policy Platform, or perhaps be a subgroup under the Steering Group on Health Promotion, Disease Prevention and Management of Non-Communicable Diseases.
    - This body should operate in collaboration with the Board of Member States of ERNs on any ERN-relevant issues, and with the Policy Board under the European Joint Programme for Rare Diseases Research for research-related matters

- This body should promote specific opportunities and avenues for collaboration and crosstalk between countries linked by geography, size, language, or other relevant considerations, to enable a tailored approach to tackling the challenges posed by rare diseases

At the National level:

- The elaboration, implementation, evaluation and renewal of robust and effective national plans and strategies for rare diseases must once again be embraced as a key policy priority.
  - The European Union shall consider an updated request to Member States in connection with national plans and strategies for rare diseases, structured within the frameworks of the health and social systems
  - The aforementioned EU-level multistakeholder group tasked with overseeing policy challenges and opportunities for the full breadth of rare disease/rare cancer issues should ensure a key focus on revitalising the national plans and strategies agenda
  - Support should be provided from the European level in terms of updated KPIs for national plans/strategies and the identification and dissemination of good practices and solutions to shared challenges
  - National plans and strategies should be robustly evaluated and – in the case of time-bound policies – renewed or replaced by national authorities in a timely and transparent manner. National authorities should ensure intersectoral collaboration in the elaboration, evaluation and implementation of national frameworks for rare diseases/rare cancers, encompassing also social and holistic actions alongside the medical and research angles
  - National authorities should dedicate designated funding to implement the national plans and their constituent activities (which should include SMART objectives, wherever possible)
  - The integration of rare cancers (both in adults and paediatric cancers) in national cancer control plans should be fostered, with relevant synergies with national rare disease plans
  - National authorities should avoid subsuming 'rare diseases' into broader health strategies which reduce addressing their specificities and their strategic prioritisation and; however, where relevant strategies exist (for instance for genomics or cancer) appropriate links to the rare disease field should be ensured
  - National authorities should consider the applicability of rare diseases to the UN Sustainable Development Goals and Universal Health Coverage debates and incorporate this to their strategic agendas
  - Countries should create a Mirror Group on rare disease research, to interact with the EJP RD Policy Board on research matters, and integrate this to their national plans and strategies for rare diseases/rare cancers
  - Each renewed national cancer control plan should include relevant and specific measures for both paediatric cancers and rare cancers in adults, addressing the issues of research and access to adequate care, in synergy with national plans or strategies for rare diseases where relevant.
  - By 2025, all countries should have a 'live' national plan or strategy for rare diseases, with a dedicated multistakeholder oversight body and an annual budget separate from the wider health and social system

Policy Recommendations for Topic 2: Data Collection and Utilisation

An integrated and strategic European framework for the capture, use, and reuse of data of relevance to rare diseases must be elaborated and adopted, to unlock the potential of rare disease data for health-related *and* research purposes (which in rare diseases are often intertwined)

- The rare disease field must become a central component of the European Health Data Space, as well as research-oriented initiatives such as the EU Open Science Cloud, to support and accelerate FAIR-compliant data-sharing
- National authorities should - with support from the European level - implement integrated electronic health record (EHR) systems capable of capturing data on rare disease patients at each healthcare encounter, utilizing the Orphanet nomenclature (ORPHAcodes) to ensure visibility of patients within national health and social systems, thus building a robust and accurate longitudinal care record
- Optimal strategies for mining unstructured or differently-structured data (for instance built upon different syntactic and semantic standards) should be identified, to make best use of the myriad of data sources available to theoretically inform health and research for rare diseases
- The role of the biopharmaceutical industry in an overarching rare disease data framework must be established, as part of an ecosystem involving the European Commission, Member States/EEA authorities, ERNs, patients, the EMA, and all other relevant actors, to ensure ethical and effective public private partnerships centred around data
- Privacy Preserving Record Linkages or other solutions to federate and link rare disease data in line with GDPR should be agreed with the support of legal, IT and technical experts, and thence be promoted by European and national authorities to support the use of such solutions
- Workable governance frameworks and guidance should be elaborated to ensure that data remain able to support rare disease health and research goals under the GDPR.
- Consensus should be developed at the European - and ideally global - level, to identify and agree the most appropriate standards and ontologies for all types of data, addressing not only diagnoses and phenotypes but also treatments, quality of life, and more: these standards should be henceforth used for public and private data generated at source, including clinical (health and social sector) and research level (including registries and data repositories) data
- European and national authorities should promote the implementation of FAIR (Finable, Accessible, Interoperable and Reusable) data principles, particularly for rare disease data: they should:
    - Provide incentives which favour data sharing or at least shareability, with a standard requirement to share data from publicly-funded research - such as placebo data and data from failed trials - to inform and streamline future research: companies should be encouraged to act similarly, whilst respecting IPR
    - Financially support the GO-FAIR (Findable, Accessible, Interoperable, Reusable) Implementation Network for Rare Diseases, or equivalent body, to provide strategic community advice on FAIRification of any and all types of data of relevance to rare diseases
    - Invest in training expert data stewards able to advise stakeholders in the national territory on FAIR-compliant data management and to support individual research projects or clinical trials in preparing relevant data from the outset, for potential secondary use in future, capitalizing on the experienced achieved by the European Joint Programme for Rare Diseases
- All disease and specialist communities – centred on or in collaboration with the ERNs - should be encouraged and supported to develop meaningful datasets and data dictionaries, for health and research purposes, based upon suitable international nomenclatures for particular types of data, and these must be made publically available to support reuse of assets and greater data interoperability on a global scale

- Specific projects/funding should be initiated, involving patients, healthcare professionals, researchers and regulatory authorities, to strategically define and agree patient-centred outcome measures for rare disease and specialised care communities, using the hierarchies of the ERNs as a basis
- Sustainable funding must be secured to ensure continued improvement and curation of the Orphanet nomenclature and associated cross-harmonisation of terminology, in line with the *EUCERD Recommendations on Ways to Improve Codification for Rare Diseases in Health Information Systems*

A renewed multistakeholder dialogue is required, at the regional, national, European and global levels, to ensure a more strategic approach to the creation and connectivity of rare diseases registries and data repositories, at all levels.

- The *EUCERD Recommendations on Rare Disease Patient Registration* remain robust and very valuable: they should be promoted by national authorities and all rare disease registries should strive to implement them
- An appropriate forum should be created/designated at the European level to ensure multidisciplinary and strategic 'oversight' of the topic of rare disease registration, in its broadest sense, and should be open to all stakeholders (including ERN representatives, European Platform on Rare Diseases Registration, European Commission, national policy-makers and/or national rare disease registry owners, patients, regulators, and Companies: this forum should:
    - advance discussions on the optimal ways to develop or orientate existing and/or future national and regional registries for (all) rare diseases, with flexibility to support working groups between countries facing similar challenges in view of size, geography, or other relevant characteristics
    - be supported to clarify the different types of rare disease registries, the possible functions and added-value each can bring, and the kind of data collection or access is required for particular purposes, to support a more strategic future for rare disease registration in Europe
    - support the sharing of best practices, to propose solutions for future national plans and strategies for rare diseases to advance or initiative rare disease registration, considering the wider European or global context as appropriate
    - consider mechanisms to incorporate direct patient-reported data to registries, and enable access to a patient's own data
    - propose and assess mechanisms to make EHRs and registries/other data collections interoperable, to foster the reuse of health data for secondary purposes.

- The European Platform on Rare Disease Registration should provide guidance and assistance to current or prospective registries in Europe (whether established by ERNs or not) which register with the Directory of Registries, supporting them to contribute to and share in the broader registry data ecosystem in collaboration with the European Joint Programme for Rare Diseases
- A dedicated body, building on the achievements of the European Platform on Rare Disease Registration and the EJP RD, should be able to advise any (current or prospective) registry owner/curator as to what the GDPR means in reality for registries and data collection/sharing.
- The EMA should provide more strategic scientific advice at early stages to companies developing therapies in the same space, directing them toward existing disease registries wherever possible (via collaboration with the ERDRI Directory of Registries), and providing impartial support for public private partnerships for rare diseases which meet the needs of all actors involved
- Decisions on new and renewed European funding for rare disease registries should be made following cross-DG, EMA and ERDRI input and advice from a dedicated EU-level forum on rare disease registration, as above, to enhance strategic alignment and reduce duplication

The unique potential of European Reference Networks to consolidate and streamline a European health and research data ecosystem for rare diseases and highly specialised healthcare must be realized through tangible actions:

- The future ERN health data strategy must be anchored to the wider European health data and IT ecosystem, driven by a concerted policy action of all the relevant DGs and aligned with national health data strategies from the majority of MS/EEA countries; in this context, ERNs should help to shape the future Health Code of Conduct for secondary use of data (addressing the need to make GDPR research-friendly)
- The future ERN data strategy must be targeted towards all rare disease patients in Europe, and not only those attending ERN HCPs: opportunities must be created for patients to foster robust data partnerships, determine governance, and contribute/extract data to or from appropriate registries, care records and other relevant data sources.
- ERNs should be financially supported to co-create (together with the European Joint Programme for Rare Diseases) a comprehensive data strategy and implementation plan by 2023, envisaging the necessary activities across 6 action lines: architecture - cloud computing services and IT support for registries and other databases; data collection protocols; data curation services; data management tools (services and tools to search, access and share data, tools to manage own data); data analytics tools and services; and a data governance framework.
- Data from hospital EHR (electronic health record) systems should be interoperable with the ERNs' Clinical Patient Management System (CPMS), and with ERNs' new epidemiological registries, allowing minimal data entry and maximum automation (with accompanying quality assurance) - all such systems should be aligned with the European Health Data Space.
- Disease-specific registries (where positively evaluated by ERNs based on rigorous criteria OR created anew by ERNs in future) should be interoperable with the new ERN registries and any robust national RD registries: these should all be connected (sustainably) to ERDRI and the European Joint Programme for Rare Diseases Virtual Platform to provide a fully functioning registration ecosystem
- ERNs should sit at the centre of all future efforts to refine and evolve all ontologies and standards for data collection and utilisation into a common data model, including efforts to facilitate extraction and mining from real-world data

Policy Recommendations for Topic 3: Availability and Accessibility of Orphan Medical Products and Medical Devices

Revising Current Regulatory Frameworks on Orphan Medicinal Products

In general:
Pan-European – and ideally global – action is necessary, to improve a currently unsustainable and inequitable status quo regarding the availability and accessibility of orphan medicinal products

- Existing resources to address the current challenges should be implemented, by national and European-level authorities, including the *EUCERD Recommendations on the CAVOMP Information Flow* and the recommendations in Breaking the Access Deadlock
- IRDiRC Recognized Resources and recommendations to improve accessibility and availability should be utilised at national and regional level, to encourage cross-country and ideally global action necessary for a paradigm shift
- EU Member States and all relevant EU authorities should revisit the actions defined in the Commission Communication and Council Recommendation concerning orphan medicinal product accessibility and availability, where these have not been addressed
- The positive aspects of the current EU regulatory framework governing pharmaceuticals for orphan diseases should be sustained, to continue to incentivise investments, whilst simultaneously increasing the robustness and transparency of the ecosystem
- Regulators and competent authorities must ensure that adaptive pathways and rapid access mechanisms continue to bring medicines to patients who need them, providing essential safety and efficacy considerations are met.
- Voluntary and early dialogue between stakeholders and countries to collaborate on coordinated access should be continued via initiatives such as the Mechanism of Coordinated Access to Orphan Medicinal Products (MoCA).
- Orphan Medicinal Product developers should consider both the individual value of products for patients but also the wider societal value, weighing the burden of lack of treatment against investments
- Orphan medicinal products should be developed, launched, and monitored within a continuum of comparative evidence generation spanning the whole product lifecycle and patient journey, enabled by a more strategic and standards-based approach to data sharing and federation centred on multi-purpose disease registries and all other relevant data sources: the application of agreed standards to increase the FAIR-ness of relevant data sources (including adequate codification of health records, to support a health innovation ecosystem) will be essential

To improve availability:

- National, European and global authorities should ensure that the development of future therapies for rare diseases is not hampered by an increasing Industry focus on distinct subgroups and mutations of otherwise common conditions under the growing trend for precision medicine

- Therapy developers - whether from the private, public or civil society sectors - should be encouraged to utilise expert rare disease resources and guidance to optimise the development and launch of orphan medicinal products (e.g. IRDIRC Orphan Drug Development Guidebook (ODDG))

- A more coherent strategy should be agreed at European level to unite relevant actors in *repurposing* of medicines for rare diseases, building on the work of the STAMP expert group, IRDiRC and others

- Regulators should ensure real-time publication of information concerning the status quo of available medicinal products and products in development for rare diseases, to expedite the decision-making process for therapy approvals

To improve access:

- National HTA bodies should ensure transparency of the decision-making process and criteria regarding orphan medicinal products
- Post-marketing HTA decisions and reports for orphan medicinal products should not take place on a country-by-country basis, but at a pan-European (and sometimes, ultimately, global) level

- In the case of advanced therapies for the rarest diseases (those affecting fewer than 1 /100,000), an EU-Fund should be established to co-finance the generation of post marketing authorisation evidence across EU Member States during the years initially following approval, in order to reduce uncertainties

- A dedicated body to facilitate EU collaboration in HTA should be established, via an EU Regulation (binding for all), but failing this on a voluntary basis as soon as possible, involving as many countries as are willing to collaborate to further the interests of their citizens and share data and assessments on the HTA of orphan medicinal products

- Actions must be agreed, at European level, to optimise the ecosystem concerning pricing of orphan medicinal products, in order to bring medicines to those who need them and reduce bureaucracy and delay in launching products at national level, whilst ensuring profitability of the rare disease market for companies:

    - Companies should be encouraged to adopt a more open and transparent approach to publicising development costs – without jeopardising core business models - in order to support pricing decisions, enabling a reasonable return on investment which supports profit-making for the private sector but does not debar patients from actually accessing therapies at national level

    - A continuous and value-based approach to pricing should be implemented, involving all stakeholders and sitting within a continuum of dialogue and evidence-generation initiated as early as possible in the developmental pipeline: a robust data ecosystem should support a move towards performance-based pricing in which products which do not show long-term benefits may be removed from market but those performing strongly may warrant their launch prices (recognising that repurposed therapies which have already recovered significant R&D costs may require different consideration)

    - In conjunction with the activities recommended for MoCA above, the EMA and payers should utilise early dialogue/conversations to provide recommendations on - initially - the basic price range which could be considered acceptable for certain types of orphan medicines

    - A workable system should be developed at European level to economically regulate the relationship between public buyers and companies, via a European Table on pricing and negotiations: this is particularly urgent in order to ensure access to advanced therapies such as gene therapies

        - A European-level pilot should support more global discussions here, which are in fact essential to improve access to medicines and therapies for very rare conditions for all

patients who need them, leaving nobody behind: the momentum created by the COVID-19 crisis should be leveraged, as an example of feasibility and collective strength of cross-country negotiations and collaborations for the greater good of citizens

The advanced therapy medicinal products hold promise for the treatment of a variety of rare diseases: specific EU-level actions must be taken to support the availability and accessibility of gene, cell and tissues therapies, which will become more numerous in future:

- Cross-country collaborations should be put in place, to streamline access to advanced therapies for rare diseases, avoiding the requirement for patients to fund significant costs upfront (or else private funding collections/crowdfunding should be encouraged for the therapies entering the markets)
- As above, proposals for a shared European fund for advanced therapies' reimbursement should be developed, to support the practicalities of patients receiving care in a different country (ensuring hospitals receive funds from agencies in different Member States in a reliable and timely fashion, for instance)
- In the case of advanced therapies for the rarest diseases (those affecting fewer than 1 /100,000), an EU-Fund should be established to co-finance the generation of post marketing authorisation evidence across EU Member States during the years initially following approval, in order to reduce uncertainties
- The precise role European Reference Networks (ERNs) can play in facilitating access to advanced therapies should be explored - and where relevant, enacted - ranging from supporting more experts and informed decision-making concerning which patients would benefit from which therapies, to actually providing advanced therapies in a limited number of centres across Europe, and collecting monitoring data

Data sources capable of supporting the launch and post-marketing assessment of orphan medicinal products must become more interoperable and federated through a continuum of evidence generation

- The myriad ways in which the potential for real world data to inform research and development and post-marketing surveillance must be clarified, and new coherent coherent strategies implemented
- Post-marketing surveillance for orphan therapies should be organised at the European level, through quality-assured shared data registration platforms/disease registries
- Efficacy as well as safety data should be collected from patients on compassionate use programmes and pooled at the European (and where possible global) level, and be made available to companies to incorporate to evidence datasets, where appropriate
- The role and capacity of ERNs in generating, collecting and analysing real world data to enhance the availability and affordability of orphan medicinal products should be further defined and adequately supported

(Additional recommendations pertaining to the potential for data to improve the accessibility and affordability of therapies can be found in the chapters dedicated to 'Basic, Clinical, Social and Translational Research for Rare Diseases' and 'Data Collection and Utilisation')

Solutions to improve the development, accessibility and availability of medical *devices* for rare diseases should be proposed and examined at the European level, and where appropriate, implemented

- The benefits of a European process for the conditional approval of devices intended for use in rare diseases should be established, accompanied by plans for a robust and shared data-collection and data-submission system.
- The advantages of European legislation incentivising the development of medical devices intended for rare diseases should be weighed, including the relative advantages of a centralised review for devices intended for orphan use.
- Notwithstanding the benefits created by the Medical Device Regulation 2017/745 (MDR), the remaining lack of transparency around the clinical evaluation assessments performed by notified bodies should be addressed, and greater cross-talk should be encouraged – at least with respect to rare diseases - between the national bodies in charge of assessing pharmaceuticals, on the one hand, and devices on the other
- The current silo between post-approval data for orphan medicinal products and medical devices used by people with a rare disease should be addressed, to develop harmonised data collection plans of benefit to regulators, notified bodies and HTA professionals
- Entrepreneurial efforts to develop medical devices for people with rare diseases should receive research and development (R&D) and regulatory support, especially if patient-led
- Particular focus should be placed on the development of devices to collect and convey data from the home environment, which should be positioned within the broader telemedicine strategy
- The potential for ERNs - and patients - to influence the design and creation of medical devices for rare diseases should be ascertained, along with their suitability for post-launch data collection on effectiveness

Policy Recommendations for Topic 4: Basic, Clinical, Translational and Social Research for Rare Diseases

Greater prioritisation and strategic support for rare disease research

At the European and global level:

- European cross-sectoral partnerships in rare disease research should be sustained, particularly under Horizon Europe, to ensure continuity for the European Joint Programme for Rare Diseases.
- More streamlined collaborations should be ensured between European Commission Directorate Generals (particularly RTD, CNNECT and SANTE) as regards rare disease research, to reduce bureaucracy and continue to strategically align rare disease funding programmes, avoiding duplication
- Strategic approaches employed in rare disease research should be considered a model and/or use case for broader health and research domains
- Resources should be designated to foster research and development in very rare and disregarded conditions which lack therapeutic options: the benefits of new incentives for this group of diseases (ideally with a global reach) should be explored.
- Funding bodies world-wide should develop globally-reaching research opportunities for the rarer diseases, with dedicated resourcesMore investments, prioritization and incentives should be ensured for basic and clinical research in areas where these are lacking - research funders must address the significant gap in basic research and discovery science for rare diseases, and simultaneously build more bridges to translate innovative and promising research from bench to the clinic and back.
- The merits of designating a European body to identify and elucidate the unmet needs of disregarded rare disease groups should be explored, as part of the mission to address the research and therapy development gaps for all conditions
- European and global research programmes and funding bodies should ensure better accountability and coordination of current funding to minimise waste and avoid duplication of efforts
- A robust regulatory science agenda (building on the existing EMA agenda) should be developed and financially supported at European level, with particular attention to the specificities of rare diseases, emerging technologies and advanced therapies.
- Research pertaining to communities with natural synergies to rare diseases must be conducted collaboratively: in particular, cross-talk and collaboration in the paediatric sphere must be ensured between European Joint Programme for Rare Diseases and Conect4Children, and all relevant future organisations
- Initiatives and grants supporting trans-national research collaborations for rare diseases must continue to strengthen incentives for the newer EU Member States (EU 13)
- Investments into public private partnerships operating in the pre-competitive space should be increased, with greater coordination and collaboration between funding sources and across sectors, and with particular attention to tech-intensive and other advanced approaches
- Repurposing of therapies for rare diseases should be supported at the transnational level, as a strategic priority

In addition, the following recommendations are proposed to ensure greater strategic support and prioritisation for rare disease research at the national level:

- Countries should take all necessary steps to meet the International Rare Disease Research Consortium (IRDIRC) Goals and implement the recommendations issued from IRDiRC Task Forces.
- National authorities should ensure that national plans and strategies for rare diseases as well as national cancer control plans for rare cancers – which should be evaluated and renewed, if time-bound - include specific goals and plans to facilitate research, and should address the following:
    - Future plans and strategies should highlight the services available to researchers in-country through the ESFRI (European Strategic Forum of Research Infrastructures) Infrastructures and through the help-desk of the European Joint Programme for Rare Disease Research, and should provide guidance on how to access these respective services
    - Dedicated funding and/or a plan of tax incentives should ideally be stipulated in the plan/strategy, to facilitate rare disease/rare cancer research either in-country or on a trans-national basis (or both), and should be proportionate to the size and situation of the country
    - National Mirror Boards for rare disease research (that also include rare cancers) should be created, to ensure a bidirectional dialogue with the European Joint Programme for Rare Disease Research and future European Partnerships

Accelerating excellent science in the rare disease domain, to maximise competitiveness

Specific support for research that will expedite the discovery of rare disease mechanisms into direct benefits for people living with rare disease is required.

- Research funders should support researchers to gain access to existing national, European, and global-level resources, infrastructures and networks, to ensure future research takes note of acknowledged best practices and avoids reinventing wheels: these should include facilitating access to rare disease-relevant services available via the European Strategic Forum of Research Infrastructures (ESFRI) and through the help-desk of the European Joint Programme for Rare Disease Research
- Research funders should insist upon greater reproducibility of data, for all stages of rare disease research, and should follow leading publications by increasingly assessing the robustness of strategies for data management, interoperability, reproducibility and sharing/linkage when evaluating proposals
- There should be a requirement to share data (at a minimum metadata) from publicly-funded research, once complete, to inform and streamline future research: patient organisations and Industry should be encouraged to act similarly, whilst respecting intellectual property rights
- Researchers should be encouraged and incentivised to publish data from 'failed' basic or clinical research; companies must publish data from 'failed' clinical research, to inform future research
- Research funders, regulators, and academic/scientific organisations must adopt and promote a new paradigm as regards incentives and rewards for research into rare diseases: an open and collaborative approach must be incentivised, favouring the publication of research results in a manner that enables discovery rights to the researcher whilst enabling access to the research data as promptly as possible (stepping away from esteem indicators based solely on competitive publications)
- Greater investments are required, to transform -omics investigations into improved diagnostics, care and treatment knowledge
- FAIR data stewardship should be available to support individual research projects or clinical trials in preparing relevant data from the outset, for potential secondary use in future - the costs for this should be included in the initial funding proposal, to ensure all results are FAIR-compliant.
- All public and private stakeholders involved in the therapy development cycle should consider the IRDIRC Orphan Drug Development Guidebook and utilise the materials and recommendations therein when approaching academic, patient-led, and industrial drug development

- Facilitate developers in continuing the development of orphan medicines abandoned by other entities for commercial reasons.
- Embed, in the regulatory landscape, proven approaches to utilizing shared platforms and innovative trial methodologies capable of targeting multiple rare diseases at once and developing therapies for multiple conditions
- The applicability of AI to enhance myriad types of rare disease research should be ascertained through dedicated projects
- Investments in all areas of innovation should be guided by large observational research utilising real world evidence, to demonstrate real-world impact of research outputs (including therapies) for patients
- Initiatives should complement the creation of expert resources to improve rare disease research by providing more accessible, direct, stakeholder-specific training opportunities; in particular, research funders and research bodies should invest in training and mentoring of junior scientists, to facilitate their familiarisation with the rare disease research pipeline and R&D processes
- Member States should ensure that all clinical trials ethics applications are assessed within stipulated timelines, to accelerate study start-up, which is essential for research into medical conditions which are severely debilitating and/or life threatening and for which therapeutic options are limited or non-existent.
- Competent authorities should harmonize the requirements in terms of pre-clinical data and documentary packages for cross-national clinical trials

Linking Clinical Care to Research - Optimising Capacity of European Reference Networks

ERNs must be supported by Member States/EEA countries and at a centralised research support structure at the European Level to fulfil their potential, as key components of a coordinated research ecosystem performing high quality collaborative clinical research that complies with the expected standards required by regulatory and Health Technology Assessment (HTA) bodies

- European Reference Networks should receive earmarked -and adequate- funding through European programmes to conduct clinical research and trials (involving centres inside or outside of the Networks, as required) and to research neglected topics including rehabilitative, holistic and social research
- European Reference Networks should be specifically and adequately funded to develop and conduct natural history (and where possible accompanying biomarker) studies, a minimum of 5 every 2 years, to build the knowledge base and capacity for clinical research in disregarded diseases/areas lacking research
- The Coordination and Support Action funded by the H2020 programme to support the creation of Clinical Research Networks (covering 4 domains: clinical research (including PCOMs); data management; engagement and dissemination; and administrative support) should be supplemented by additional funding to deploy core services to become fully operational by 2025
- Collaboration between the European Reference Networks and global entities, such as the NIH Clinical Research Networks, should be supported
- European Reference Networks must collaborate with their relevant scientific and learned societies, in discussing research priorities, in order to build synergies around activities pertaining to rare diseases
- European Reference Networks' potential to positively impact the development and use of medical devices for rare diseases should be explored
- European Reference Networks should receive funding to employ research-oriented staff to complement their clinical experts, particularly for HCPs in countries where research capacity-building is most needed
- Clear rules are required that enable European Reference Networks to collaborate with industry across a range of pre-agreed activities, clarified and tested through pilots, using shared SOPs to

accelerate research and build mutually-agreeable public private partnerships: a central business development/tech transfer office could promote, coordinate and supervise European Reference Networks interactions and agreements with industrial partners

Placing patients at the centre of clinical research

Placing people living with and caring for someone with a rare disease at the center of clinical research, drug development, and evaluation is increasingly recognized as paramount to fully understanding a disease and to identifying meaningful endpoints. Their knowledge, contribution, empowerment, and participation are crucial to increasing the efficiency of such efforts. **Specific recommendations on partnering with advocacy organisations and people living with and caring for someone with a rare disease are elaborated in the section on Patient Partnerships of this document**.

Socially-oriented research into rare diseases

Both cross-border and national foci are required to prioritise and advance socially-oriented research into rare diseases:

- The European Commission should increase funding opportunities to assess the true impact (clinical, social, personal, and financial) of rare diseases through collaborative research
- The European Commission should support proof of concept studies to demonstrate how preventative, integrated care can result not only in better quality of life but also in economic savings
- The European Commission should support research to assess and publicise the respective levels of functioning and disability associated with rare diseases, through a publically-available database accessible for all (for instance through expansion of the Orphanet Disability Project or similar)

Additional Recommendations to improve integrated and person-centred care for people with rare diseases can be found in the chapter on Integrated and Person-Centered Care.

Bridging the research and development divide for rare diseases

Concrete actions and strategic directions are required in order to optimise the regulatory pathway for would-be therapies and devices for people with rare diseases. Therapy development, which is a cornerstone of rare disease research, should take place within a cohesive, multistakeholder ecosystem. Recommendations to steer the European rare disease community in this direction are elucidated in the chapter on Available, Accessible and Affordable Treatments.

Policy Recommendations for Topic 5: Diagnostics

Better use and accessibility of existing solutions, within a more strategic and coordinated diagnostics ecosystem

Obtaining a timely and accurate diagnosis is a human right, whether there is an available medical treatment or not. The following steps should be pursued to better apply existing tools, best practices and programmes

At the European and global levels:

- A clear, systematic and European-wide (indeed sometimes global) approach to rare disease diagnostics must be ensured, founded upon the ability to guide patients towards centres of expertise or equivalent, access transnational diagnostics platforms, and capture - and systematically manage - data on patients for whom a diagnosis is not forthcoming
- Continued support must be ensured for multinational and multistakeholder research linking omics data, clinical data and biomaterials with well-defined patient cohorts and applying them in the clinic, building on the work of existing initiatives such as the EJP RD and Solve-RD
- Existing and future best practice guidelines to support the diagnosis of rare diseases (such as decision trees and patient pathways) should be visible and findable at the European level (via ERNs and Orphanet) and should be adopted and implemented to a greater degree at the national level
- The Orphanet services pertaining to diagnostics (resources concerning the definition and inventorying of diseases, and the database on expert clinical centres and laboratories) should increasingly be co-created and co-curated together with ERNs, and should be sustained by European action
- Funding bodies in Europe and all other world regions should target diagnostics for subpopulations, indigenous people, and other culturally and linguistically diverse populations in a culturally safe manner (including populations in developing nations): this will support the genetic and phenotypic characterisation of rare disease populations to enlarge patient cohorts and advance knowledge and understanding.
- Appropriate and targeted funding should be dedicated at EU and national levels to foster research into aetiology of rare diseases with no evident underlying genetic causes
- Research should be fostered at European level to elucidate the determinants of the heterogeneity across EU Member States in terms of diagnostic performance
- Research should be fostered at the European level (inline with the *Commission Expert Group on Rare Disease Recommendations on Cross-Border Genetic Testing*) to conduct a cross-border health economics assessment of diagnostic and screening technologies, comparing costs and benefits relative to those currently incurred under the diagnostic 'odyssey'

At the national level:

- Countries should define clear national strategies to support RD diagnostics and should support professionals involved in diagnostics -and through them, patients- in their national territory to access specialised diagnostic platforms; in particular, to utilise genome-phenome platforms and similar tools suited to rare disease diagnostics, especially those recommended by IRDiRC now and in the future for diagnostic purposes
- Countries should strive to meet the IRDiRC goal stating 'patients with a suspected diagnosable RD should receive an accurate diagnosis within 1 year of coming to specialist medical attention' and indeed should

treat this as a minimum, reduced to 6 months or less in the case of conditions for which a preventive strategy demands neonatal or infant diagnosis.

- Countries should fully implement the provisions within the *Commission Expert Group on Rare Disease Recommendations on Cross-Border Genetic Testing*
- Countries should adopt, and provide the means (financially and organisationally) to actually implement EU level best practice recommendations on diagnosis and screening
- Countries should ensure an available and appropriately trained workforce to address rare disease diagnostics in the clinics of the future
- Countries must ensure that genomic and rare disease diagnostics services promote cultural awareness of all populations, including indigeous populations and other culturally and linguistically diverse populations, approaching diagnoses with sensitivity and ensuring appropriate coordinated and integrated care

European and national authorities must take action to reduce the inequalities stemming from the existing heterogeneity in national approaches to screening and prevention of rare disease, and collaborate to support more informed and transparent decision-making for primary and secondary prevention

- The proposed activities highlighted in the *EUCERD Opinion on Newborn Screening* should be revisited and implemented through a European-level body or programme; new solutions proposed in EURORDIS Key Principles for Newborn Screening should be considered
- Countries should work collaboratively to share best practices and HTA data concerning newborn screening programmes
- The cost-effectiveness of newborn screening should be calculated and set against the costs of the diagnostic odyssey and costs to the health and social systems in the absence of an accurate diagnosis
- An EU level recommendation on NBS should be created, addressing the following: the potential of genome sequencing for newborn screening; the need for screening panel expansion to be based on scientific advancement and health technology assessment; the recognition that screening is not just a test, but rather a process which requires adequate communication with families and the public; adequate training for healthcare professionals; and more
- A greater focus on preconceptional prevention and care for rare diseases is required, encompassing primary prevention and screening, the need for improved communication with affected persons and family members, a greater emphasis on professional awareness and alertness, the need to ensure regular disease follow-up, and more. Regarding primary prevention, the *Recommendations of EUROCAT and EUROPLAN on Primary Prevention* should be revisited

Linking Better Diagnostics to Care Pathways

National and European authorities must place particular strategic emphasis on reducing the diagnostic 'odyssey' from primary care to specialised diagnostic support, by establishing and ensuring care pathways to most efficiently accompany people living with a rare disease from diagnosis to highest quality care and where possible to the European Reference Network (ERN) covering the disease.

- Individuals with suspected diagnoses must be referred to the most relevant specialist centres/ centres of expertise / coordination hub at the earliest opportunity: the precise role which ERNs could play in facilitating a diagnosis for rare disease patients lacking one should be clarified and better implemented at the national level.

- Governments should identify and implement optimal methods to share electronic health records (which include rare disease-specific data elements) across borders, in order to increase diagnostic efficiency
- Countries should prioritise the raising of awareness of rare diseases in primary care (essential for effective triage), focusing on the following:
    - Healthcare professionals must be encouraged to refer more readily when unsure of a patient's pathology– they should be encouraged to 'know what they do not know'
    - Countries/health systems should explore and invest in symptom-checking suspicion prompt tools in primary care settings, designed to raise 'red flags' and guide doctors towards specialised therapeutic centres to streamline the diagnostic odyssey
    - As triage to identify a possible area of specialism for referral rests upon awareness in primary and secondary care of how and where to access such expertise, national referral pathways to tertiary centres of expertise (or a catch-all coordination hub/centre for rare diseases) must be elucidated and made publicly available
    - Mandatory medical training for all healthcare professionals should include education on rare diseases, including the following concepts: the specificities common to all rare diseases, and subsequent challenges; the main sources of information on rare diseases; the ways in which national and cross-border systems for rare diseases have been set-up; the unique value of research; and the considerations for diagnosis, treatment and care.
    - Online training and accredited courses in rare diseases should be made available to primary care workers

Strategic collaboration to address the needs of undiagnosed patients

- Countries should implement the *International Joint Recommendations to Address Specific Needs of Undiagnosed Rare Disease Patients*
- Countries should build knowledge on existing undiagnosed rare disease patient populations – research should be conducted to establish number of undiagnosed patients, and socio-economic impact including impact on patients' and families' quality of life and ability to access health and social care
- Undiagnosed patients should be properly coded in health information systems, by annotation of electronic health records with specific codes to ensure traceability and enable appropriate action from healthcare providers: the recommendations of initiatives including RD-CODE should guide and structure this activity
- Whilst patients are awaiting a confirmed diagnosis for a suspected rare disease, access to appropriate health and social services should nonetheless be ensured:
    - Cross-country explorations are needed, to assess the feasibility of a temporary diagnosis based upon clustering of phenotype and symptoms: specific codes should be added to electronic health records, and diagnosis assertions metadata should be added to ORPHAcodes, based upon the recommendations of RD-CODE and other relevant initiatives
    - European guidance on genetic counselling following a diagnosis of a rare disease -or failure to find a diagnosis in a suspected rare disease patient- should be elaborated and implemented in all countries.
    - European countries should agree on a strategy for sharing core case details and samples - leveraging existing biobanking infrastructures - for unsolved patient cases, to ensure support for their unique needs in the absence of a diagnosis, and to practically and systematically ensure repeated testing as knowledge advances.

Application of new technologies

<u>At the European level</u>

- Continued support must be ensured for multinational and multistakeholder research linking omics data, clinical data and biomaterials with well-defined patient cohorts and applying them in the clinic, building on the work of existing initiatives such as the EJP RD and Solve-RD
- Ensure European support to best research and implement modern diagnostic technologies and advances equally across countries
    - at preconception, using novel techniques such as pre-implantation genetic diagnosis
    - during pregnancy, such as maternal blood test, ultrasound or chorionic villus sampling
    - at birth, considering the potential of genome sequencing in newborn screening programmes
    - later in life, taking into account artificial intelligence and genome sequencing techniques in the expansion of screening programmes
- Robust data should be collected and analyzed on diagnostic utility, clinical utility, and cost-effectiveness while evaluating the impact of new technologies

At the national level

- Facilitate and expand access to scientific advancements such as next generation sequencing techniques, imaging, artificial intelligence and other digital solutions by applying them in a clinical setting in accordance with recommendations from consortia such as Global Commission to End the Diagnostic Odyssey for Children with a Rare Disease.
- A wider range of agreed ontologies should be deployed in health and research data capture systems, to support diagnostics and facilitate extraction and mining of information - from real-world data particularly - to evaluate the impact and facilitate reimbursement of new technologies
- Countries should ensure an available and appropriately trained workforce to address rare diseases diagnostics in the clinics of the future
- Countries should ensure a greater investment in and development of clinical (phenotypic) interfaces, to complement investment in the genomic and screening aspects of diagnostics
- Countries should ensure appropriate funding to support the translation of pilot projects on new diagnostic technologies into value-based solutions in the clinic

Policy Recommendations for Topic 6: Integrated, Social and Holistic Care for People with Rare Diseases

All people with a rare disease should be supported to participate fully and equally in society, labour, education and leisure, without discrimination and in fulfilment of their basic human rights but also in recognition of the benefits to society at large.

Policies, programmes and services to address the social and person-centred needs of people living with a rare disease should synergise with global, European, national, regional and /or local disability programmes or strategies, to build solidarity in areas of commonality, whilst maintaining a focus on the features which demark rare diseases for special attention .

People living with rare diseases, their representatives and families should contribute directly and indirectly to the design of such policies, programmes and services to ensure they are patient-centred and prioritised in terms of true needs. The disproportionate impact of rare diseases on women carers, in particular, must be ameliorated through appropriate policies across multiple domains including social well-being, employment, diagnostics, reproductive choices.

Integrated, person-centred and long-term care

Policies and practices must be designed and implemented to ensure a local, regional, national and European focus on identifying and addressing the social and holistic needs of people with a rare disease: more integrated care (both in terms of integration across medical disciplines but also bridging the medical and social spheres) should be provided for rare and complex diseases

At the European level:

- A common definition and indicators concerning person-centred care - bridging health and social domains- for people with rare diseases should be defined at European level, through a future Council Recommendation or similar, in view of the specificities and knowledge-gap associated with rare diseases, which necessitate a European approach
- Financial and structural support should be allocated to ensure the sustainability of relevant Europe-wide platforms including the European Reference Networks, the European Network of Resource Centres for Rare Diseases and Orphanet. These platforms gather and share essential knowledge and good practices that support countries to effectively address both the health and the social needs of people living with a rare disease. An enabling environment should thus be created to integrate these initiatives with national health and welfare systems.
- The European Commission should support a dedicated initiative or body to collect and review concrete good practices for ensuring an integrated and holistic approach to care for rare diseases, and to assess the impact of different approaches and interventions in a structured and systematic manner
- European Reference Networks and the Board of Member States should embrace a strategic mission of promoting more integrated care, encompassing integration of different medical specialities, but also of paramedical and social actors, in line with the *EUCERD Recommendations on Rare Disease European Reference Networks* and the *Commission Expert Group for Rare Diseases Recommendations to Support the Incorporation of Rare Diseases into Social Services and Policies*
- A cross-ERN working group on integrated and person-centred care should be established (by 2025) in partnership with European Resource Centres for Rare Diseases, as a gateway to build joint guidance on collaborative approaches for the provision of integrated and person-centred

care to people living with a rare disease: dedicated funding should be made available for broad stakeholder meetings and activities to advance this goal

- ERNs should gather and create - in collaboration with patient organisations - resources and data which could support rare disease patients in receiving more and better adapted integrated and more personalised care in their local environment: such resources should translate to heterogenous care and social settings, by focusing on clarifying and explaining the (often poorly-understood) needs of patients with complex conditions, and adaptations/approaches which could help patients; making use of digital tools where needed and helpful
- The European Commission - in collaboration with the European Network of Resource Centres for Rare Diseases - should raise particular awareness of the need for cross-border collaboration between specialised disability centres dealing with 'rare disabilities' such as sensory deficiencies or intellectual disabilities, promoting the identification and sharing of best practices and exchange of knowledge
- The European Commission should increase funding opportunities to assess the true impact (clinical, social, personal, and financial) of rare diseases through collaborative research as referenced in Recommendation 10 of the *Commission Expert Group for Rare Diseases Recommendations to Support the Incorporation of Rare Diseases into Social Services and Policies*
- The European Commission should support proof of concept studies to demonstrate how preventative, integrated care can result not only in better quality of life and grant people living with a rare disease the right to the standards of health and social care they are entitled but also in economic savings; sharing this evidence base widely
- The European Commission should support research to assess and publicise the respective levels of functioning and disability associated with rare diseases, through a publically-available database accessible for all (for instance through expansion of the Orphanet Disability Project or similar)

At the national level:

- Countries should invest as needed to fully implement EU level standards, infrastructures and tools including the existing consensus recommendations and resources concerned with the social and holistic needs of people with rare diseases, namely the following:
    - The *Commission Expert Group for Rare Diseases Recommendations to Support the Incorporation of Rare Diseases into Social Services and Policies*
    - Recommendations of the INNOVCare project
    - The recommendations within the EURORDIS Position Paper 'Achieving Holistic Person-Centred Care to Leave No One Behind' (which were built upon past European projects including the EUCERD Joint Action and RD-ACTION)
- In view of the fact that national plans/strategies for rare diseases should structure activities within health *and* social systems, bodies intended to implement, evaluate, and/or renew these plans/strategies should involve representatives from both Ministries of Health, Ministries of Social Affairs, Welfare, Labour or equivalent and Ministries of Education, to support a multidisciplinary perspective.
- National plans/strategies for rare diseases should provide dedicated funds to encourage the bridging of health and social care and enable holistic wellbeing (encompassing also educational - including transitional- and employment opportunities) along with other incentives to encourage coordinated care across-sectors (with a particular focus on the opportunities offered through eHealth, cancer plans and data strategies)
- Countries should set aside more resources to cover or reimburse the costs of non-pharmacological therapies including preventative, rehabilitative and palliative care (when supported by best practice guidelines in peer-reviewed literature)
- Countries should ensure that the concept of a centre of expertise within the national territory (including ERN HCPs) is as aligned as possible with the *EUCERD Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases*, including also the requirements to ensure multidisciplinarity and to collaborate with paramedical, social, and educational actors

- Countries should ensure that all centres of expertise for rare diseases (including ERN HCPs) in the national territory include a patient care coordinator or case manager role – these positions should be accompanied by an official career pathway, in terms of qualifications, (continuous) training and salary, and should support patients in accessing the health and social care they need, closer to their home: the INNOVCARE training resources can be instructive here
- Countries should ensure robust networking between centres of expertise for rare diseases and specialised disability centres addressing 'rare disabilities' such as sensory deficiencies or intellectual disabilities: such networking may need to take place on a cross-border basis, in the absence of domestic centres, in which case national authorities should facilitate the sharing of best practices and exchange of knowledge

Equal opportunities and access to the labour market

- All EU and national level legislation must guarantee that there is no form of discrimination based on health or disability status. The Horizontal Equal Treatment Directive should be swiftly adopted and any discrimination on all grounds covered in the Article 21 of the European Charter of Fundamental Rights, and in all fields, should be tackled.

- All legislative proposals and recommendations deriving from the European Pillar of Social Rights must take into account the specific needs of people living with a rare disease, their carers and others with complex diseases/disabilities.

- The 'Social Scoreboard' should introduce clear indicators that reflect the reality on the ground and monitoring tools to support effective policy changes.

Active support to employment

- Access to high quality education must be guaranteed to all people living with rare diseases and complex conditions. When necessary, adapted schooling should be accessible and delivered in a way that supports all individuals to reach their maximum potential.
- Tailor-made assistance to improve employment or self-employment for people living with rare diseases, such as career counselling to explore fulfilling professional avenues, is needed.
- All EU and national level legislation must guarantee that there is no form of discrimination based on health or disability status, concerning all forms of employment, including recruitment, hiring, employment, career advancement and safe and healthy working conditions. The Employment Equality Directive must be fully implemented with targeted support via EU funds, appropriate legislative frameworks, and exchange of practices to support the labour market integration of groups in disadvantaged situations as part of active labour market policies.
- Access to social protection measures, pension rights and care support must be guaranteed for people living with a rare disease, their carers and others with complex conditions when leaving the labour market or having to work part-time due to the disease.
- Measures to ensure people living with a rare disease and with disability who wish to study and/or to be active as volunteers for civil society organisations, are in no way deprived from their rights, including disability and retirement benefits.

For fair working conditions

- European countries, via the implementation of the Work-Life Balance Directive and other means, must ensure that people with complex conditions/disabilities and their carers have the right to specific mechanisms that support their access and retention in the labour market:
    - Flexible work arrangements, such as flexible working hours and remote work;

    - Reasonable leave of absence due to their health/disability condition or caring responsibilities;
    - Reasonable accommodation in the workplace.
- The European Commission should provide MS with the necessary support to ensure the full implementation of Directive (EU) 2019/1158 on work-life balance for all parents and carers of people living with a rare disease who need those provisions.
- The European Commission should provide guidelines for MS on how to ensure reasonable accommodation for people living with a rare disease in the workplace, in line with Article 5 of Directive 2000/78/EC. The guidelines should encourage MS to entitle people living with a rare disease with adequate leave of absence and flexible work arrangements, in line with the provisions offered to parents and carers within the Directive (EU) 2019/1158 on work-life balance.

Social protection:

- The future EU Child Guarantee must fully integrate the challenges of children in most vulnerable situations, as is the case of children living with a rare disease, or suffering from a cancer or surviving a childhood cancer, guiding EU and national policy frameworks and financial resources to ensure adequate resources for childcare and early intervention services;
- EU MS must implement specific mechanisms to guarantee coordination between national policy sectors within a multidisciplinary approach, engaging health, social, work, education and research Ministries. Inter-Ministerial working groups and shared budgets between Ministries should be implemented;
- The future European Strategy on the Rights of Persons with Disabilities must provide guidance to Member States on disability assessment procedures to ensure persons with all types of disability, including persons with rare conditions or multiple impairments, are not overlooked and are provided with adequate levels of disability allowance, social protection schemes, community-services and independent living arrangements;
- A Convention on the Rights of Persons with Disabilities (CRPD) Unit should be established within the European Commission, placed in the EU Directorate General for Justice and Consumers, under the supervision of the EU Commissioner for Equality. This unit would be responsible for the implementation of the UN Convention on the Rights of Persons with Disabilities and for coordinating the work of all disability focal points in EU institutions;
- EU MS must guarantee that all people living with a rare disease and their carers are entitled to access a social worker and adequate social protection and social inclusion provisions, adapted to their individual needs and to the cost of living;
- The “right to be forgotten” should be enacted in national legislation: medical information relating to rare diseases or cancers should not be collected or held by insurance organisations for longer than ten years following the end of treatment (five years in the case of paediatric patients)
- Patient organisations also provide specific support, information and counsel to patients, their families and carers along the patients’ journey. Their social action should be supported by European and national authorities.

Policy Recommendations for Topic 7: Rare Disease Patient Partnerships

All stakeholders involved in rare disease diagnostics, prevention, treatment, research, care, and holistic support should contribute to the creation of an ecosystem which fosters and rewards meaningful patient partnerships, exemplified by an ethos of co-creation and exceeding mere involvement, engagement, and even empowerment.

- Policy makers, physicians, researchers and all other stakeholder groups should place equal value on the work and contributions of rare disease patients and carers, acknowledging the unique services and insights they provide
- More meaningful and equitable patient partnerships must become the gold standard in all health-related activities, not only in research but in all relevant domains ranging from care delivery to policy making:
    - Concrete indicators should be developed at European -and where relevant, global- level, to measure the success of patient partnerships in the respective activities; in the case of research, these should build on the outputs of the PARADIGM IMI 2 project
    - Stakeholders should appreciate the absence of a strict 'one size fits all' model for rare disease patient partnerships, and be prepared to adapt approaches as necessary
    - Robust and concrete examples of meaningful patient partnerships in each domain should be disseminated globally
- National competent authorities should ensure meaningful patient partnerships in the elaboration, implementation, monitoring and evaluation, updating of national plans and strategies and other relevant policies for rare diseases, or measures for childhood cancers and rare cancers in adults in national cancer plans, and in all activities stipulated therein
- Policy makers, physicians, researchers, patients, and all other stakeholders should recognise that robust and equitable patient partnerships cannot exist when services, time and expertise are bestowed without remuneration; consequently, they should ensure a fair and transparent system of financial support and compensation (which will simultaneously broaden representation by removing the current *de facto* requirement for independent financial means)
- Policy makers, physicians, researchers and all other stakeholders should give particular thought to accessibility when building patient partnerships in rare diseases, considering not only barriers such as language, but also accessibility requirements for those with learning disabilities, hearing and/or sight impairments, etc.
- The ability of people living with a rare disease (and their carers) to fulfill essential advocacy roles and build patient partnerships is hampered by the disproportionate challenges they face in all walks of life, from psychosocial difficulties to financial, educational and employment-related barriers; therefore, the provision of adequate holistic support for rare disease patients and carers that encompasses social care and adequate social policy measures, should be a priority for national competent authorities seeking to support an ecosystem in which patient partnerships can thrive

European and national authorities should provide strategic, cohesive and sustained support to perfect and scale-up robust training activities and programmes supporting patient partnerships in the rare disease field

- European-level training to understand how to form effective patient partnerships in the rare disease domain should be further elaborated and scaled-up, comprising bespoke elements for patients/families/carers, on the one hand, and for researchers and health-related professionals on the other, with opportunities for joint stakeholder training

- European-level training in 'core skills' for rare disease patients/families/carers should be further elaborated and scaled-up, with an emphasis on building confidence and fostering strategic, diplomatic, and decision-making competences for those aspiring to leadership roles
- Patient organisations should ensure particular emphasis on engaging and building capacity in the next generation of young patient advocates
- National authorities should consider endorsing and utilising the training courses and materials provided by groups/initiatives such as the EJP RD, EURORDIS, and EUPATI - which espouse best practices for rare disease patient partnerships as agreed at the European level - by supporting their implementation and facilitate their access at national level, in the national language
- Although it is essential to provide specialised training on how to build and sustain meaningful patient partnerships in the rare disease and highly specialised care field, the value of patient partnerships should nonetheless be emphasised by relevant national authorities in more generic training and education programmes for care, research, and policy-related professions at large.

The potential for ERNs to embody robust patient partnerships, internally and indirectly by spreading good practices and resources, should be fully realised:

- ERNs should develop clear and transparent rules for patient engagement, adequately supporting the involvement of patient organisations and their representatives in the different ERN activities and fairly compensate patient representatives
- Within ERNs, opportunities must be created for patients (not only those attending ERN healthcare centres) to foster robust data partnerships, determine governance, and contribute/extract data to or from appropriate registries, care records and other relevant data sources
- ERNs should be supported to review and expand their disease-specific membership criteria, in partnership with patients and professional associations, with an emphasis on the necessary multidisciplinary expertise: in this way, EU countries (perhaps even the global RD community) could make use of robust criteria by which to define expertise in given disease areas
- ERNs should gather and create, in partnership with patient organisations, resources which could support rare disease patients in receiving more integrated and more personalised care in their local environment: such resources should translate to heterogenous care and social settings, by focusing on clarifying and explaining the (often poorly-understood) needs of patients with complex conditions, and adaptations/approaches which could help
- ERNs should encourage the development of - and adherence to - codes of conduct and Terms of Reference for ePAGs and patients representing wider communities in ERN-related roles.
- ERNs should help to promote a culture of **shared decision-making** in the patient-physician relationship, encouraging professionals in ERN healthcare providers and 'affiliated' centres to discuss all options with regard to the treatments and approaches available, empowering patients to make more informed decisions in partnership with their care team.

Tools, resources and good practices to develop robust and equitable patient partnerships in rare disease research should be elaborated and implemented

- The principles of the EJP RD Short guide on patient partnerships in rare diseases research projects should be noted and implemented by researchers and research funders

- The Patient Engagement Toolbox created by the PARADIGM project should be implemented by researchers and research funders, to assess patient capability, avoid conflicts of interest, support patients in managing competing interests, assess fair market value of patient services, amongst other benefits.
- The Guiding Principles on Reasonable Agreements between Patient Advocates and Pharmaceutical Companies should be more widely used. This multi-stakeholder initiative aims to make legal agreements between both parties easier and more acceptable while providing adequate protection and rules for both sides. Patient partnerships should span the full research and development pipeline, including the preclinical stage: researchers and research funders must support patients and patient representatives to *shape* the research agenda, identifying research priorities and knowledge gaps and contributing to call texts, in addition to partnering in research once underway; the Joint Transnational Calls of the EJP RD exemplify good practices in building patient partnerships in rare diseases research, and can be viewed as a good starting model for improvement
- Patients and researchers should ensure two-way communication and collaboration to improve patient partnerships in rare disease research: researchers should involve patients in activities such as organisation of conferences, publications and seminars (to help educate and inform other researchers about the added value of patient partnerships), and patient organisations should involve researchers in family days, conferences, newsletters and other appropriate activities
- To complement training activities designed to build capacity and confidence for patients wishing to participate in research, specialised training should be provided to *researchers*, funded by research bodies and initiatives, to demonstrate how to engage rare disease patients in the full cycle of research activities and build mutually beneficial partnerships
- By 2030, following incremental demonstration of the added-value of patient partnerships in the rare disease field, patient organisations should routinely and systematically be considered and included as full partners in any basic, preclinical, clinical, translational, or social research
- Targets for patient partnerships in research activities and research events should be agreed, based on agreed metrics (building on the outputs of the PARADIGM IMI 2 project)
- Patient partnerships should be considered a fundamental cornerstone of translational research for rare diseases: evidence of robust patient partnerships should be available as part of the Marketing Authorisation process for all orphan medicinal products
- The achievements and resources of initiatives such as EFPIA and the EURORDIS Community Advisory Board (CAB) programme, aimed at developing policy principles and codes of conduct to guide Company-Patient interactions, should be sustained
- Industry, researchers and patient organisations should explore a transparent working model (or models) to provide baseline financial support for rare disease patient organisations to organise and achieve their core goals whilst remaining independent and maintaining credibility

Policy Recommendations for Topic 8: Access to Healthcare

Given the breadth and depth of the topic 'access to healthcare', several categories of recommendations are required, directed towards different actors:

a) Recommendations for a more strategic and directive European role in enabling access to high quality healthcare for rare and complex diseases
b) Operational recommendations to lead Europe towards optimal ERNs of the future
c) Recommendations at the national level, to optimise access to care at national level and support more seamless cross-border care for all patients requiring it

a) Recommendations for a more strategic and directive European role in enabling access to high quality healthcare for rare and complex diseases

- Greater pan-European, and indeed global, collaboration is called for to address the health inequalities citizens face in accessing highly specialised healthcare in the EU, in particular the EU should develop a Health Framework for Rare Diseases, that formalising MS collaboration in strategic and workforce planning and decision making to develop and manage a European highly specialised healthcare system, where ERNs are the operational arm for delivery.
- Pan-European policy should be elaborated to ensure the centralisation of care and expertise, for the rarer diseases, to organise care pathways, based on prevalence and incidence levels, and to commission services on an optimal population size to ensure safe and sustainable services are accessible for all.
- Shared resources should be developed for commissioning and contracting designated European Centres of Expertise, for rarer diseases and highly specialised interventions that affect an annual national caseload of <250 to be accessed by all affected individuals.

b) Operational recommendations to lead Europe towards optimal ERNs of the future

- The strategy of future ERNs must be targeted towards all rare disease patients in Europe, and not only those attending ERN HCPs or 'affiliated' centres: ERN operations (from guidelines to data collection, knowledge generation to research) should always target this wider population, wherever possible
- A common EU agency should be created/adapted to enable ERNs to operate more flexibly and effectively, and receive funding from a range of sources (including 'external' sources such as industry and private donors, with an appropriate governance for public-private partnerships)
    - As many believe ERNs should ideally each be legal entities, they should – as an interim solution, at least - be nested within such an organisation, or a foundation, to provide a mechanism for ERNs to easily receive funds.

- ERNs need a long-term funding framework which should consider ALL possible sources of funding: such a framework needs to be defined urgently and should include a definition of all central functionalities and policies to support ERNs' financial management and governance

- The realistic costs of network coordination, relative to the activities of the ERNs, should be established, and coordination funding provided on these grounds – a core coordination budget, available to all ERNs, should be supplemented by an additional variable budget, based on size, scale, coverage and activities
- A special category of association or collaboration or affiliation should be created to allow formal collaboration and recognition of centres from countries outside of the EU Member States /EEA; clear rules on shared activities (what is and is not permitted) should be created

- ERNs and the BoMS should embrace a strategic mission of promoting more integrated care, encompassing integration of different medical specialities, but also of paramedical and social actors, in line with the *EUCERD Recommendations on Rare Disease European Reference Networks* and the *Commission Expert Group Recommendations to support the incorporation of rare diseases to social policies and services*
- The European Commission should support Member States and EEA countries to implement the actions outlined in the *ERN BoMS Statement on Integration of ERNs into national health systems*, specifically by funding national multistakeholder workshops, with patient organisations, clinical leads and national authorities, to facilitate discussions and actions on integration into each of the national health systems.
- ERNs should develop strategies to minimise disparity between European regions in access to high quality healthcare: disease-related metrics should be agreed and monitored
- A robust focus on continuous monitoring of ERNs is required, to demonstrate their impact: the EU-monitored indicators should be supplemented with more nationally-relevant and disease-relevant indicators
- ERNs should develop clear and transparent rules for patient engagement, adequately supporting the involvement of patient organisations and their representatives in the different ERN activities, and should fairly compensate patient representatives for expenses and expertise.
- ERNs must be supported to educate and train the future experts in rare diseases, in terms of clinical training, surgical training, and also training in holistic care and wider wellbeing
- ERNs should be supported to review and expand their disease-specific membership criteria, in collaboration with patients and professional associations, with an emphasis on the necessary multidisciplinary expertise: in this way, EU countries (perhaps even the global RD community) could make use of robust criteria by which to define expertise in given disease areas
- A cross-ERN working group on integrated and holistic care should be established as soon as possible, in partnership with RareResourceNet (the European Network of Resource Centres for Rare Diseases), as a gateway to build joint guidance on collaborative approaches for the provision of integrated and holistic care to people living with a rare disease: dedicated funding should be made available for broad stakeholder meetings and activities to advance this goal
- ERNs should gather and create, in collaboration with patient organisations, resources which could support rare disease patients in receiving more integrated and more personalised care in their local environment: such resources should translate to heterogenous care and social settings, by focusing on clarifying and explaining the (often poorly-understood) needs of patients with complex conditions, and adaptations/approaches which could help
- A dedicated study/project should be funded, to support countries in developing their Electronic Health Records and virtual care delivery services to best address the specificities of rare diseases and highly specialised healthcare, and promote interoperability: this could aim at wider national deployment of the CPMS or a system compatible with it, as the basis for virtual care provision for complex rare disease cases nationally (whilst ensuring that any move towards more virtual care must be proportionate, to avoid further marginalization of a vulnerable population).
- The Clinical Patient Management System (CPMS) should be fully compatible with any referring HCP systems, enabling automatic and two-way cross-talk with Electronic Health Records, to populate and update records post case referral: CPMS data should be fully searchable, and cases accompanied by an appropriate PPRL (privacy preserving record linkage) solution
- An efficient project/tender should be funded to establish a pricing model to reimburse expert time spent on CPMS case review and propose options for payment (e.g. a *quid pro quo* system, a straightforward billing of another Member State/EEA country (perhaps with a differential GDP-based pricing scheme), a reduction in the workload of ERN HCP clinicians in lieu of payment for CPMS reviews, etc)
- The Social Security Regulation and/or Cross-Border Healthcare Directive should be amended to allow for payment of time spent on cross-border virtual consultations performed through the CPMS, following a systematic national referral process

- Countries should consider automatically authorise requests for treatments or therapies if deemed beneficial by an ERN panel through CPMS: the ERNs' expertise should hold more weight than national expert bodies who make such decisions at present

c) Recommendations for national authorities, to improve access to care at the national level and create an environment supporting seamless cross-border care for all patients as required

In terms of optimising national ecosystems broadly:

- The elaboration, implementation, evaluation and renewal of robust and effective national plans and strategies for rare diseases must once again be embraced as a key policy priority at national and European levels
    - The European Union should consider an updated request to Member States in connection with national plans and strategies for rare diseases structured within the frameworks of the health and social systems
    - The aforementioned multistakeholder group tasked with overseeing policy challenges and opportunities for the full breadth of rare disease issues should ensure a key focus on revitalising the national plans and strategies agenda
    - Support should be provided from the European level in terms of updated KPIs for national plans/strategies and the identification and dissemination of good practices and solutions to shared challenges
    - National plans and strategies should be robustly evaluated and – in the case of time-bound policies – renewed or replaced by national authorities in a timely and transparent manner
    - National authorities should ensure intersectoral collaboration in the elaboration, evaluation and implementation of national frameworks for rare diseases, encompassing also social and holistic actions alongside the medical and research angles
    - National authorities should dedicate designated funding to implement the national plans and their constituent activities (which should include SMART objectives, wherever possible)
    - National authorities should avoid subsuming 'rare diseases' into broader health strategies which reduce their strategic prioritisation; however, where relevant strategies exist (for instance for genomics or cancer) appropriate links to the rare disease field should be ensured
    - National authorities should consider the applicability of rare diseases to the UN SDGs and Universal Health Coverage debates and incorporate this to their strategic agendas
    - By 2025, all countries should have a 'live' national plan or strategy for rare diseases, with a dedicated multistakeholder oversight body and an annual budget separate from the wider health and social system
    - National authorities should carefully assess medical education and training materials designed to support professionals in providing an optimal standard of care to people with rare diseases; where appropriate, resources generated at European level, representing best practice, should be recommended for national use (including educational resources emerging from the ERNs and Multidisciplinary Joint Committee of Rare and Undiagnosed Disease (MJC RUD) at the European Union of Medical Specialists)

In terms of greater support to -and integration of- ERNs:

- Renewing or updating national plans and strategies for rare diseases should remain a key priority for all countries - all such documents should stipulate the strategy to engage bidirectionally with ERNs: support in this task should be provided by a group/body with a remit to encompass all rare disease topics, beyond ERNs alone
- Countries should be encouraged to revisit and update their national designation of Centres of Expertise (CEs) for rare diseases and strengthen the organisation of national rare disease and specialised care networks - this should then translate to a more strategic engagement of national CEs with ERNs, via a limited number of full member HCPs.

- The concept of a Centre of Expertise for rare diseases should be revisited/affirmed at national level: countries should ensure they designate all such centres in a comprehensive and transparent way, and make the result of such a mapping and designation publicly available, demonstrating how ERN HCPs and 'affiliated' centres fit within wider national networks (where applicable). The *EUCERD Recommendations on Quality Criteria for Centres of Expertise for Rare Diseases* remain a robust resource here and countries should aim to meet this, to support a baseline comparability in quality criteria
- National competent authorities should define national referral pathways for rare disease (or suspected rare disease) patients or those requiring a concentration of expertise, addressing transition from paediatric to adult care and containing clear guidance on how and when to seek referral to an ERN; ERNs should then compile and publish these pathways, explaining the process in each country and producing -with their patient advocates- patient-friendly information and advice on accessing specialist advice under an ERN.
- All Member States and EEA countries should identify and publicise a clear process to facilitate the referral of patients for ERN care: this might include endorsing one centre as a 'National Coordination Hub' (or, if a federated system, endorsing a centre in each region, or in several strategically-selected regions) to manage referrals and function as gateways to accessing the specialist advice of the ERNs collectively - any such centre should work in partnership with the national patient community, and build relationships with national professional societies and research leads
- The European Commission should provide coordination funding to coordinating HCPs but Member States /EEA countries should provide funding to each national HCP/affiliated member within their national territory (providing they meet performance and impact indicators) to support their engagement in ERN activities
- Hospitals must strengthen support for the participation of their clinicians and other professionals in ERNs
- Each Member State and EEA country should define a mechanism, centred upon Orphanet, for instance, to disseminate and utilise the knowledge and evidence generated by the ERNs, to impact across the wider health and social systems; in particular, clinical practice guidelines/clinical decision support tools generated or endorsed by an ERN should be fully applied in all Member States and EEA countries, and national committees and structures dedicated to rare disease or specialised healthcare should include some level of national ERN HCP representation

Recommendations on the role of ERNs in data gathering, research and innovation

ERNs must be provided with the financial, technical, political and operational support required to collect and use findable, accessible, interoperable and reusable data as a means to support the accelerated development and uptake of treatment options for rare diseases and integrate European-wide clinical research and care settings. **Specific recommendations have been included throughout this report in respective sections pertaining to research and data.**

Annex 1: Policy Consultation with the Panel of Experts on Topic 1 (Political & Strategic Frameworks Relevant to Rare Diseases)

a) Do we need a new action plan or EU policy framework for rare diseases? (Should the 'founding' policy documents -primarily the 2008 Commission Communication and 2009 Council Recommendation- be supplanted by new 'soft legislation' or do they simply require more effective and meaningful implementation?

Comment/Response
I think more effective and meaningful implementation is needed. I see that nationally as well as internationally administration is going slower and slower :(sometimes I think while it takes them time to implement one law, we need to change it since it got old …
So far, EU countries acted in response to EU documents on RDs and policy was adopted (see the whole map showing the status quo as of May 2019). Lack of policy implementation is the problem. Putting the NP/NS into effect is difficult at national level without a guidance and budgetary allocation to assist the process of implementation.
It might be useful to start an update process of existing documents, like with guidelines to establish a more continuous process of improvement.
We have a lot of good legislation so perhaps the problem is not with this, although *hard* legislation would be helpful - would compel countries to act. We need more effective and meaningful implementation of some of the 'soft law' documents still, in many countries

The first commission communication and council recommendation were quite successful as soft legislation. It was successful *because* it was soft legislation. After that, we tried more hard legislation, like the cross-border directive. This contained provisions that made it possible for national authorities to somehow make but not really implement a cross-border directive. We can also see what is happening now with work to support collaboration on a European level when we talk about HTA cooperation. That is also very difficult as it contains obligatory points. Therefore, even though this kind of legislation is soft legislation, it may be the most effective as it still puts pressure on national authorities to live up to the recommendations and they have to report back

Agree that we have very good laws around Europe and we have very good coverage for Europeans affected by rare diseases in some countries. We need a more clear picture of how the existing laws (soft or otherwise) have been implemented in different places, and especially we need to have a better picture of how all of the MS actually follow patients through the health system . Although the cross-border directive generated the ERNs through Article 12, the recent auditors report shows the application of that Directive is still far from ideal.

There have been significant advances across almost all of the areas included in the Commission Communication, including eHealth, technology, diagnostics and primary prevention. The text under those headings now seems quite antiquated. There is therefore a question about how well it addresses not just the technologies but also the *regulatory structures*, for example around data sharing and registries. That suggests that there may be benefit in reviewing and updating the documents across the board

There is some good information on eHealth, but we need to consider whether we need to do something more. We hear not just about eHealth, data, and registries, but about artificial intelligence and this may open up new ways to diagnose rare diseases or for clinical trials. We should push to modernise the concept of artificial intelligence in eHealth

A recent publication from the European Court of Auditors recommends including ERNs more explicitly in these sorts of legislative recommendations. This report recommends better assessment of the results of the 2008 and 2009 policies and sets out more explicit ways of addressing the challenges faced by the ERNs and perhaps simplifying the structure and creating recommendations on whether they should be updated, adapted or simply replaced. This provides a solid basis upon which we can justify an updated legal framework.

In this project, we could produce a recommendation or similar on specific topics where ERNs feel they would like to have something consensus-driven to clarify their needs and opportunities for particular areas. We also need to look at what topics might be missing from earlier policy documents (such as the 2008 Communication) and/or do not have recommendations, which nonetheless are important for rare diseases in this day and age.

Any revisions or new policy documents should emphasise collaboration with patient organisations .

Patient engagement as a Theme is quite prominent in the Council Recommendation. It specifically asks Member States to do certain things, one of which is support empowerment of patient organisations. However, this does not necessarily mean that it is being implemented everywhere or that it contains enough detail

From the point of view of a patient organisation, we are moving from the terms of engagement and empowerment towards terms like partnership, where patients are becoming much more proactive actors in the process. Rather than having this issue siloed in these types of soft laws, spread the integration of patient input and activities under *each* heading, throughout these types of documents. There has also been progress in including patient input in tertiary prevention, as well as primary prevention in beginning to study how quality of life and patient reported outcomes could help us have a better understanding of quality of care

It can be quite abstract to discuss whether we need another piece of 'soft' legislation if we do not have a consensus on where we are and where we want to go (and what the challenges are). If we haven't achieved what we set out to do in the soft laws then an 'update' would need to include the same topics, more or less. But if we feel that we have achieved major progress on a particular aspect, we could have a different focus and might move forward. One concern is that the outside world is starting to consider our field as too successful, and research is starting to head down the path of 'all diseases will be rare in the future'. If these fears are grounded, we might need a completely different approach to RD policies (and different types of national plans).

In thinking of our future strategy, it is useful to remember the origins of the soft law documents. In 2008/2009 the Commission was required to create two documents; the Commission Communication and the Council Recommendation. These are quite different documents in terms of what they aimed to achieve. The Commission Communication sets out what the Commission should do and the Council Recommendation is really about what the Member States ought to do. It's normally very difficult to persuade the Commission to produce two documents like this, which was the main problem in 2008/9: and this would be an even greater challenge now, especially due to the current priorities of the Commission. Politically it would probably be best to aim at a Council Recommendation instead of a Commission Communication, providing we have the complicity of at least one of the Member States holding the Presidency of the Council during the semester (e.g France in 2023). It would be useful to develop a roadmap to that presidency.

The "founding" policy documents of 2008 and 2009 have still value - it would be great if they could be revitalized and reinforced in many of their objectives, such as

- National Plans- ensure renewal and adequate funding, aim for unlimited plans, rather than time bound
- Leverage practices - France keeps being mentioned- mechanism of early access (like ATU) should be the praxy for rare diseases (granting access whilst under approval/gathering evidences) and for advanced technologies with curative possibilities
- Foster even more research on rare through cross-border cooperation
- Consider and emphasize more the ERNs: how to fully integrate them in national healthcare, national plans and how they can facilitate cross border healthcare
- Reinforce the concept of access to "high quality healthcare" vs access to medicines only
- Reinforce the efforts to increase collaboration at EU level for scientific assessment of added therapeutic value (for example the EC legislative proposal on HTA and the approach on joint clinical assessment as a way to accelerate time to patient access with quality methodology)
- Explore additional incentives at national or EU level to strengthen research: " incentives" could mean better alignment between EMA and payers on end-points, which factually signify a streamlined development process, better use of high quality registries, better frameworks for RWE data in regulatory decision making for rare
- Focus on Art 9 of Reg 141/2000

The needs for expertise centres has not been addressed sufficiently, which is a major concern. The creation of ERNs has actually created a lot of confusion in this respect, at different levels. At national level, the policy makers are pointing towards the ERNs and using them to justify why no further efforts are needed to create expertise centres at national level – this seems to be the case in Belgium and most likely in other countries. When speaking with some clinicians they highlight this as a major challenge, as if a centre is not part of an ERN there is a growing feeling they are not a 'real' centre of expertise. One perceives a growing 'two-tier' tension. Furthermore, from a patient perspective there doesn't appear to be concrete progress at ERN level yet. A major step forwards would be to better recognise expertise centres and stimulate national authorities to begin creating expertise centres/designate the existing expertise better (whether formal members of an ERN or not). The excuse that it would cost too much shouldn't stand in the way of making it visible.

VH: Agreed, the visibility is not there. The Council Recommendation asked all Member States to identify their centres of expertise and to map these and designate by 2013. In an ideal world this would make it easy to see what expertise we have for which conditions, and would have facilitated the designation of HCPs for ERNs. However, we have a sort of patchwork since some centres officially part of the ERN were formally designated by their country as centres of expertise and have gone through a precise auditing process, whilst in other countries due to short timelines some centres were designated as ERN HCPs but not centres of expertise per se, and didn't go through the other process of being formally recognised as a centre of expertise (it is important to emphasise that all ERN HCPs should in theory meet shared horizontal criteria). But overall, many feel that there is a bit of a mismatch and tension here, in a way. It is important to remember perhaps that the idea was never for a single network to include every centre in Europe that has expertise in any of the relevant diseases. Every CE does not need to be a full HCP member of the ERN. The idea is that maybe a couple of the centres would be part of the network but then there would be a visible national system/network where you can view *all* of the centres of expertise for a specific disease and they collaborate and communicate with each other

Confusion persists in many countries of what is expected of a HCP when they become a member of an ERN. Many just want the label but it isn't just about being an expert in a certain field: they also need to contribute to the network and so they must have appropriate medical time to contribute to the aims of the network (CPMS, conferences, etc). Therefore, I strongly agree that this needs to be arranged and supported resource-wise at the national level (either that or expert centres receive compensation for work). The issue has been discussed several times at the ERN Coordinators meeting - we cannot keep increasing the number of HCPs because this will be impossible to manage in the end. If the network on a European level has to deal with every sub-specific problem of a given patient for the whole of Europe then this will never work because there's no medical time for this.

There is an issue around the definition of rare disease vs rare cancers. Two projects have worked to provide a definition on rare cancers with a rationale as to why a different definition is needed.

The final conference of the Joint Action for Rare Cancers will be an opportunity to summarise the needs and conclusions of the rare cancer field into a proposal of best practices, which can be conveyed to the Steering Group on Prevention and Promotion.

One of the major problems is that the development of the ERNs on one side and the Centers of Expertise in the National action plans for rare diseases on the other side are not really and sufficiently linked together, not really connected. ERNs and Centers of Expertise must realize that there is no competition between them, but that they both follow the same goals and have to work together better than now. To facilitate this might be a worthwhile activity for the national authorities, achieving the integration of both in the national healthcare systems.

I think that the centres of expertise are a national competency and responsibility and the ERNs are by their nature transnational. While a high degree of overlap is likely (and desirable) it should not be surprising that there is not a perfect fit and in many ways nor should there be. As ERNs grow then this should become less of an issue but we must be careful not to force the ERNs to do too much too quickly, especially with current resourcing levels

As one of the main challenges for people living with a RD is lack of coordinated services, future action plans could focus on how to implement rights/regulations on coordinated services and individual plans for all patients (rare and not rare) with complex, chronic diseases in the different countries. Together with developing national CoE and the ERNs, such rights/regulations would benefit RD patients who need multidisciplinary/ multi professional services.

b) How do we sustain -or revive- momentum around the implementation of National Plans and Strategies for Rare Diseases?

Comment/Response
We need to revive it. I would recommend public awareness campaigns for rare disease day in all countries, to let the public, media, institutions. Where we were, where we are and where we need to be.
The Council Recommendation of 2009 was not mandatory but asked countries to elaborate on the national plan and strategy by the end of 2013 at the latest. There is no similar document or push for countries to develop a plan for 2019, or to evaluate successes or failures. The potential for things to be diluted, for rare diseases to move into other groups of health-related issues, can be seen as a threat.
We have already noted that in 2019, we do not have any Expert Groups for rare diseases. We do not have a group or a joint action at the European level for rare diseases. New groups have been established, but they have a broader remit. We have the ERNs and the ERN Board of Member States, but their mandate is to focus on ERNs. The ERNs are very important and are the anchor for rare disease activities, but not everything fits under the ERN remit. So, there is no obvious forum to discuss these sorts of issues *All the specific groups in the Commission referring to rare disease policy have disappeared or been replaced by a single structure steering group. However, this steering group on promotion and prevention has the ability to create subgroups... (though only composed of Member States, no patient organisations or other groups).* Indeed, one output of this rare2030 project will be a proposal to the Steering Group *Patient organisations are really keen to have NP/NS plans implemented. We need to find other instruments but need to come up with a continuity of a multi stakeholders forum to discuss European policies at national level*
Some national plans and strategies will have an end date eg, the UK strategy ends 2020 and is in any case quite moribund. Hopefully Rare2030 will prepare the ground for a renewed commitment and act as an incentive to refresh of the national strategy and plans where existing ones are outdated or have run their course.
The legislation is good. There is an open-ended process in Germany but they have implanted a national rare disease plan and action plans where rare diseases are prominent. However, there is now no money to fund this. The best centre for rare diseases cannot function if there is no money *It is also important to agree what we consider a 'plan'. A plan is something that has clear actions, funding and a monitoring process. In some cases, funding is for new actions, which is why we cannot implement existing actions. We have to distinguish between these two types of funding.*
The assumption of rare disease under other domains is one of the single biggest risks as there will only ever be partial coverages. It is important to integrate into other strategies and plans, but it is critical to maintain a very dedicated plan around rare diseases. Implementation of things such as genomic plans are holding back development of rare disease national plans in countries that do not yet have one *It is risky to incorporate rare disease into broader areas.*
The European structures could consider applying the open method of coordination to the field of rare diseases and complex conditions. That would initiate a more structured approach. The open method of coordination has

been used by the European Union in employment, pensions and social inclusion. Member States submit national action plans on a regular basis. The European Commission pulls together all of the reports and issues a European level report showing how countries are implementing certain policies. An important factor in using this method is that it needs to be monitored. Indicators are defined at a European level to measure progress. The Commission makes recommendations to Member States in the fields it feels it should concentrate on, in order to make progress. This is soft law, but it clearly shows the progress made by Member States at a European level. The results give patient organisations evidence they can take to their national governments to try to effect change. ERNs are trying to spread information to other countries using new technology such as the CPMS. The technology exists for surgeons based in the UK to do procedures on patients elsewhere. The technology is there but the ethical, regulatory and other frameworks are not keeping up.
Stimulate to revive and update the plans seems essential; and add a solid reliable governance; even the plans that are 'so-called' continuing plans (without end-date) do not necessarily continue towards further implementation. The fact that they don't have an end date can be an excuse to actually not have the plan executed/implemented yet and not have to report back on what has been done. Even the information gathered by SOTAR is not a guarantee for reliability on what had truly been done (e.g. the mentioned stipulated 15M Euros per year for execution of NP in Belgium is something that is never accounted for clearly when asked after).
In Romania, there is a policy-decision to ensure a dedicated budget for national programs for RDs (Ministry of Health - 15 dietary treatment programs for RDs and National Health Insurance House - 14 curative treatment programs for RDs) but no financial support for other specific areas such as Centres of Expertise and Registries. Countries should assess their needs for support and assistance of implementation process and new EU Commission 2019 should have a role to play moving forward with implementation. Rare2030 can offer practical solutions to solve the problem providing direction worksheet for new EU Commission.
In the list of currently involved stakeholders. I did not see the UEMS, European Medical Associations and Universities and Medical Schools and Medical quality improvement institutes, which have also updating programs and implementation strategies which might be of help.
The ERNs are a good model for how we should manage collaboration, networking and implementation of complex disorders. The EC is placing a lot of emphasis on the integration of ERNs into national health systems. But of course ERNs were not included in some of the previous laws, policies, and recommendations (e.g. National Plans/Strategies for RD), so some of these may need updating to reflect this. For instance, Italy is currently writing the new rare disease plan and they are still not including the ERNs. I agree, Maurizio, but this places a heavy burden on the ERNs that not all are able to discharge effectively. And then there is the real problem of how to maintain or even improve standards whilst reaching out and being inclusive. As I have said verbally at the meeting - ERNs have the potential to be the answer to everything but trying to do everything is a recipe for disaster. Some tasks need to be assigned elsewhere for now even if the long term strategy is to migrate them into the ERN structure when it has capacity to absorb them
The Board of MS of ERNs has recently been discussing the integration of ERNs into each Member State policy for rare disorders. They agree about revising the plans to incorporate the needs of the ERNs.
Rare cancers are not addressed in national rare disease plans. They are addressed in very few cancer plans, since cancers are treated in oncology centres. Therefore, there is a big gap for rare cancers (paediatric and adult) and a need to incentivise Member States to include rare cancers in their cancer plans. Member States also need to make relevant links between their cancer plans and national plans for rare diseases since rare cancers share many similarities with rare non-oncological diseases.
We need to keep communicating around the topic and have champions: 1) The meaning of rare disease is lost - we need to keep reminding that rare disease is not just prevalence or incidence - it is a broader concept and ultimately we are talking about people. The meaning of rare disease is

broader than the single criterion of prevalence. It is about the high unmet need, the lack of scientific knowledge, the isolation of patients.In addition it has to be noted that the question may be erroneously informed, given - according to COMP - prevalence is a functional expression of incidence and duration (to quote COMP: under the assumptions of stable incidence and duration of the condition, the functional relationship between point prevalence (P), incidence (I) and mean duration (D) is commonly expressed as P = I x D. It follows that the definition of the duration of a condition is of particular relevance for the estimation of prevalence).Therefore arguing that incidence (instead of prevalence) should be used may restrict the definition especially for long-duration diseases, which will still remain rare in their essence and will go against a very scientific, proven and consolidated approach.

2) Need to continue talking about rare diseases from a human perspective - let's stay what we are, human

3) Need to clarify the difference between rare diseases and personalized medicine to avoid decisions badly informed

4) We need to remember the importance of rare as setting the way scientifically and organizationally for new models applicable for other diseases - rare gives a lot to science and society, there is a lot we can learn from rare and this per se should position rare at the top of the list

The question to me is why countries are not implementing the plans - it is just for budget reasons?

Need to keep highlighting the general subject of rare diseases and scientific progresses. A lot of these general scientific breakthroughs and advances are very beneficial to rare diseases and can be used to attract attention. For a lot of Member States, they are a matter of pride and they can tend towards international collaboration

First of all let me emphasize again the importance of the integration of ERNs into the national health systems.

This means:

a) That hospitals and physicians must become aware of the competence of ERNs;
b) That health care authorities and insurance companies accept their task to take care of sufficient funding of the work of ERNs and Centres of Expertise for rare diseases;
c) But as well we all should make all efforts to enable the health care providers themselves,, to accept, that it is likewise their own business, to strengthen the cooperation with the ERNs and the Centres of Expertise and between them both. It is not a challenge of legislation alone, but also concerning the principles of subsidiarity. So it is not solely a matter of parliaments or EU-Commission, but also -in any case in Germany - of the self - regulatory bodies;
d) On European level it could be a good idea, to create a subgroup by the steering group, but anyway with the participation of patient organisations.

This is all good but would need considerable resourcing and we have to recognise that essentially the ERN project is still a large scale pilot rather than a full working model. I am sure some will hate me for saying this, but so much is untested still that for those actively involved it feels like we are working on the cutting edge - exciting, but risky and we need to take each step carefully before moving on. Frustrating, because we all want it to be there for everyone right away.

It is required a more effective monitoring for strategies from EU. As already mentioned, comparable indicators for National Plans among countries are essential. Dose defined by EUCERD where a great job, but now after almost 10 years should be revamped and above all, must be used being scaled down to real life. Tools as the state of the art and EUROPLAN are determinant for engaging different stakeholders pushing policies and action on RD, nevertheless are not useful for benchmarking, what is very effective with policy makers and allow to make

a real map of the NS implementation on MS. Clear endpoints to achieve in a time as those address in the EU recommendations on RD in 2009 are very encouraging too. In decentralized as Spain countries a coordination hub for RD could solve the need for a budget, leaders and implementation schedule.
In Norway there is an implemented system of Centres for RD under the Norwegian National Advisory Unit on Rare Disorders. We just harmonized our definition of RD to the EU definition. The Ministry of Health and Care Services have asked the Dir of health to make a draft for the RD strategy, together with professionals and patients. Hopefully the strategy will be finished in 2020. Implementation of the strategy should start as soon as possible, including adaptation to the revised definition and inspired by experiences from EU countries. Other important areas to cover is international cooperation and implementation of ERNs in our national health care system, coding of RD, coordination of services, social care and other non-medical issues.

c) How could the European Union pave the way, strategically and practically, towards the common goal of more research, more treatments, and better quality of life for people living with RD (and thus contribute to the achievement of health-related UN Sustainable Development Goals)?

Comment/Response
Give incentive to countries that contribute towards better quality of life of people with rare diseases, specifically where there is significant progress in social services (since for a lot of rare diseases there is no treatment), and also somehow to give incentive to national researchers (from the government employees not from pharma) that work in the field of rare diseases (it can be in education and research grants)
For this Insight Study we may need to define more specifically which problems need to be resolved specifically in order to achieve a better quality of life. We all demand in our different documents that there has to “more research, more treatment, better care” etc. In order to discuss strategy we may need to specify the next steps that need to be done to achieve improvements. Comparable to the core indicators for national plans as defined by EUCERD, adapted to where we stand now and where we need to go. E.g. the route to diagnosis is still too long: with what strategy can we achieve that modern technology/artificial intelligence/use new diagnostics etc. will ensure the right diagnosis within less than a year for 95 % of people afflicted?
The EC is obliged to produce an Implementation Report on the Council Recommendation and Commission Communication every five years – the last was completed in 2014 (and should be added to this KBS, as it addresses NP/NS for RD) and the next is due this year, which is another important backdrop for this work. The new Parliament this year is also an opportunity for renewed and targeted advocacy

One major initiative is European semester and benchmarking of countries, and we don't have any indicators in rare diseases. The Steering Group on Prevention and Promotion proposed Orphacoding as best practice, so if tracking could be developed it would be major improvement.
First, EU must maintain recognition of RDs as a public health priority. Second, EU should offer financial support for ERNs.
Strikes that the Commission is a little timid because they are being criticised, but the worry is that the good things can be damaged by timidity. It is frequently cited that healthcare is a national competence but we need to do a better job at differentiating rare diseases to general healthcare. *Only* focusing on rare diseases at a national level is a nonsense and this must become a European competence. ERNs are a demonstration that this is happening but such activity is still not happening smoothly, and needs to be guided from a central European core.
Involve existing structures on education and research more in relation with updated national plans/strategies for RD such as UEMS, European Medical Associations and Universities and Medical Schools and Medical quality improvement institutes
Facilitate a stronger link between Orphanet and ERNs
The definition of what a rare condition is needs to be revisited and refined, particularly in light of personalised medicine and subsetting of common diseases into rarer groups.
• Keep building on existing frameworks instead of vanish what was accomplished • Foster multi-stakeholder policy making • Foster ERNs and "undiagnosed disease networks" • Learn from cancer community, the sense of urgency and the collaborative multistakeholder plain dialogue • Pave the way to the democratization of health at societal level: o be forward looking in the approach to data, digital, artificial intelligence thinking to the person holistically (so health technology intervention but also several other dimension of life where certain aspects can be improved or facilitated thanks to data and digital) o Start by simply work on how to increase acceptance of real world data and evidence in the approval processes • Do not mix and dilute RD in other policies
One of the main problems out of my sight is the matter of possible financial support for ERNs and - may be - Centres of Expertise by industry. Since a long time the Board of Member States discusses this question between this two poles:

a) Research, development and clinical trials are dependent on financial support by industry;
b) there may be no influence by industry on ERNs and their work, organisation and structure at all.

If the discussion finally should come to the conclusion, that funding by industry is an essential part for the work of ERNs, especially in the fields of research and treatment, then it will be inevitable to find a way, to keep industrial funding away from direct influence on ERNs and Centres of Expertise.

Annex 2: Policy Consultation with the Panel of Experts on Topic 2 (Data Collection and Utilisation)

a) What actions/approaches around collecting and using data will yield the greatest progress for the rare disease field?

Comment/Response
Involvement of patients and inclusion of QoL-related data
Extracting data from RD registries for research
A real need to drag together all of the various initiatives and the previous solid foundational work (on RD registries in particular) into a single project, or at least to ensure that strong and workable linkages exist to cut duplication and conflict between projects.
We have ca 700 registries. Some are working really well and some of those I'm sure are really not functioning at all in this day and age, so do we do about the mixed playing field that we have? Rather than throw everything away and start from scratch, I think we need to build an infrastructure that can accommodate the widest possible need for registries. *We need to find a way for those registries that are in existence that are really worth keeping, to migrate those into this infrastructure – it has to be a flexible infrastructure but it needs to be scalable. (KB highlight- I think this is of paramount importance- should be a total moratorium on reinventing the wheel- again)*
There is a need to analyse the mistakes we made in the past around registries, to allow an evolution or a disruption
As someone who may not be brilliant but certainly is not stupid, the complexities that surround the creation of successful and sustainable rare disease registries have troubled me for some years now. For me, my "Damascene" moment was that the answer must lie with the ERNs - a game-changing collaboration between clinicians/researchers and patients that should be the natural home, or at least anchor-point of **every** rare disease registry IMHO. I groan every time I hear of new registries being created without even passing reference to the ERN opportunity - for the most part these will be short-lived and at best achieve limited (often selfish) results, often for a specific treatment rather than the whole disease. However, ERNs are not resourced (yet) to take on this challenge and this must change.
We need to think more about what is the goal of each registry - if it is a registry with patient-entered data, patients need some training on how to provide that data. Also need to think of the quality control.
Need to agree on the standards to use - but not just ORDO and HPO but broader, as these are just a part of the total data set that we are going to need to do precision medicine with our patients. What about medical views, what about treatment, what about quality of life. It is very important to be consistent with the standards that we are going to use and also be consistent with the standards that the industry is using right now. This is something that the US does with the Precision Medicine Initiative.
Maybe we need to think less about centralising and siloing data in centres, and more about it sitting with patients, or at least with patients gaining access to it This does not need to be incompatible with having a robust overarching structure

We need a lot of money and time to implement good registries - but it is doable, it is just a long road
I think we have a lack of clarity on what's the battlefield what about the strategy. The battlefield for me is about the 25 million people in the EU. It's not the people in the CPMS. It's not the patients and families consulting their health care provider with an ERN. That could be the starting place. It's like the tree, but we need to go down to the branches, where the patients are in the local hospital and with the doctors. So for me, whatever data strategy we have it should try to target all patients in Europe, whether they go to the recognized main healthcare provider or not. *Yep- need to think big- look at possible partnerships with big IT tech for example- though patient/ national funder driven to ensure oversight*
Making the EU Platform for RD Registration more operational. We need to be really honest, the ERDRI has not yet succeeded in the creation of something operational from the point of view of the production of common data.
I believe there must be a way how to link data: the central registry in Latvia is definitely not capable to capture all patient related info - they have only basics - disease name and some characteristics, and there is nothing bad about creating smaller registries and apps that can capture patient everyday life with disease to derive more info from it for doctors and scientists. But I guess we need to involve some IT gurus that can show how to link up existing registries, what are the blanks they do not cover and where to improve. As said earlier, it should be under ERNs and as private-public-partnership probably
I think registries should be primarily 'contact databases' with an agreed minimum dataset, to allow for fundamental segmentation. Eg by gene type. There needs to be robust consent in place to allow for approaching patients in future and linking their data to other datasets. Eg in UK, Renal Registry to HES and Genomics. I'm not in favour of mega registries or migrating registries to some superstructure. There isn't sufficient time or resources to do that.
The approach around collecting and using data with the potential of yielding the greatest progress in the rare diseases field is converging our efforts and making best use of the structures and functionalities that have been created to this purpose. To this aim, the European Commission has developed the European Platform on Rare Disease Registration (EU RD Platform), which is conceived as a central place to be accessed by all existing rare disease registries, thus giving to participating registries the possibility to become visible in a common platform, share their data, increase the use and reuse of their data, reach the necessary number of patients for studies of any type (epidemiological, clinical, pharmacological, etc.) and research. Very important, the EU RD Platform makes registries' data searchable and findable.
One of the key considerations we have to make is who generates the data - and, in particular, how we make patients and carers generate the data where we can. This can help community-built registries, community- and patient-level data feedback and inclusion. It also expands the technology and logistics, and potential. It has implications for sure for interoperability. I also suspect it's inevitable. *This is interesting and I freely admit I have a lot to learn. Whilst philosophically I am in favour of patient input (and control) I am also wary of this approach and believe that the core of any registry needs to be clinician, or at least HCP, driven. Supplementing this information as a peripheral add-on could be attractive and workable, whilst also allowing the core to be fully inter-operable* Carrying over a comment in another workstream (devices) by Victoria (*please bear in mind I am quoting her comments from another place - this reflects my opinion that it is a salient point here, rather than speaking for Victoria*): "There are particular benefits to having better (and earlier) patient involvement in Medical Devices development: I think in a world where hopefully we are more and more aware of the benefits and the need to involve patients in the design and creation of different devices, the ERNs could act as quite a nice centralizing force." For me, I can point to a company for whom I work, developing apps with mobile devices for registries. In particular, we build these collaboratively with patients and carers (I strongly recommend we include carers in this idea. As well as proxy-completion, carers often are vital to understanding, e.g., whether and what wearables will work in children or frail elderly) - and IRBs, clinicians, etc. https://vitaccess.com/my-real-world-tm-patients But it's just one example, even the FDA has built one! https://www.fda.gov/drugs/science-research-drugs/fdas-mystudies-application-app

Building on Yann's comment below in point 2 - While Registries are important, we should consider how they fit into the larger data ecosystem. If we continue to take isolated decisions, and dedicating resources without a clear understanding of what we want to achieve in the long-term, the risk is that we will never be able to untap the full potential of health data. Progress in the rare disease research and improvements in care delivery will come only if we are able to combine different types of data that are being used and stored in different settings. So we really need to go beyond registries to get this right. What actions? 1. Re-focus the conversation, take a step back and understand how the rare disease data challenges (data collection, aggregation, curation, use, legal and ethical challenges, etc) fit into the wider health data ecosystem. After all, we do share some of the challenges and therefore solutions will be common. If we want the rare disease field to be part of the Common European health data space, we need to bring our voice to that fora. Important decisions on health data sharing (including how to make the GDPR research-friendly) are going to be taken over the next years and we if want to be part of that conversation, we need to reach out and engage with the wider health data ecosystem. 2. Build a strategic vision for health data, by starting with addressing the following question - what do we want to with the data? where is it store - it could be registries, but also EHR, mHealth apps/wearables, knowledge sharing platforms, biobanks, diaries, calendars, personal health records… ? Is it scalable - data quality is good enough for the uses that we ensage?. Engage with a wide group of experts to shape this vision - rare disease experts + bio-informaticians, ethicists, data protection experts, security and IT experts, health authorities, hospital managers, etc). 3. Use the ERNs as a sandbox for innovation/to implement the strategy Completely agree with this and the issues of data integration
Another priority area that needs to be further explored are the aspects related to health data governance. The GDPR guarantees the protection of data subjects rights but we need to articulate workable governance frameworks to make that legislation research/healthcare-friendly. We are at the point where legal services are determining what can and cannot be done, as opposed to HOW it can be done to remain GDPR compliant. There is still a need for legal, IT and security experts, to collaborate more closely to find workable solutions that respond to the needs of the healthcare sector and enables us to make the most out of the wealth of health data that is being routinely collected.

b) Many activities are ongoing to make various sorts of data more interoperable/linkable: what are we missing? Where should the next emphasis (under this vast topic) be focused?

Comment/Response
Simply to increase the number of registries is not a success in itself. What has happened during the last 10 years with the ways that have been put in place by the Commission, it has been that registers have been created by The health program by Horizon 2020 by other projects that you have very well listed in your document and for the initiative of companies, etc. There is no centralization, somebody said before that there is a centralization *There was definitely a flaw in the (still continuing!) calls for proposals that led to proliferation of independent registries and data collection and harmonisation methodologies. Many researchers duplicated a lot of effort in this and this contributed to the fragmented landscape now. It might be positive (though perhaps controversial) to have a moratorium on new registries etc until some of this is settled.*
We need a forum for national policy-makers to discuss the way to process re. National RD registries. In Bucharest we had a working group of small countries. It's much easier for us to share resources to share ideas etc is much more complicated for me in Luxembourg to share things with France. But I think that we can establish probably working groups with countries having similar problems and create something common not just during big events

but in a more constant way. We have a transnational focus for ERNs now, but not really a transnational policy focus in Europe (meaning that MS cannot share practices and priorities). Well, we know that we live in a multi-speed world, and somehow we need to find ways for the fastest and best are able to support the slower members and ERNs are a fantastic way to do this. It is not easy, however.
I think it's very important if you want to implement this policy not to forget national registries are important tools. There are several kinds of national-level registries. There are now huge initiatives on the European joint programme. Maybe we will see results in one year or maybe more. NP/NS for RD should include the national registries properly - for sustainability. And the countries need to retain focus on updating these NP/NS in the first place
We need to clarify what is the point of a national registry for rare diseases? It has a role for health delivery of course, but that is a very narrow ambition for something that by definition needs to be on a transnational basis to be effective for the main uses *E.g. in Romania, it is important to know how many patients we have in order to decide budget for neonate screening, genetic investigations, treatment (to help patients reimbursement costs.* E.g. in Italy the national registry can be used to support the assessment of ERN HCPs
A step backwards really is the Statement from the Board of Member States of ERNs on forbidding Industry from partnering in registry development, I*s it a step backwards or sideways? It was disappointing but not unexpected and the old model of industry participation has run its course in my view. However, the urgency for this to be upgraded is great and dealing with it via an ad-hoc committee approach is not able to address such a complex issue. We need intelligent and sophisticated solutions to overcome quite legitimate fears whilst still delivering the powerful registry products we desperately need.* To me, maybe we need a new way of thinking about industry participation in registries. The old way of having pharma driven registries needs to be challenged- but we should embrace the opportunity to find new ways as an overarching issue for ERNs and RD in general, not run away from this. Blanket statements like this are not necessarily very helpful
An important untapped resource is big data. Need to find a way to grow and search 'data lakes' where there is all the placebo data from clinical trials for instance *We have HTx in process now, but I am not sure this is big enough nor ambitious enough for the scale of the task and the potential for benefit. Initial noises from the new commission suggest there may be an open door for new initiatives in this area - let's hope so.*
We should try to bring back data to the patients and perhaps use new elements like the blockchain for instance, or maybe other technologies - would help to avoid more and more centralisation. I worry that Blockchain is seen in some quarters as an answer. It is an enabling technology and should be the servant of the need not its master. Let's sort out the questions and then select the right tools - this may well be one of them but we need to do it in the right order.
Need to clarify who is the owner of the data and who manages the data is an important barrier from a patient point of view to know what has happened with the information.
Need more clarity on what kind of registries we want and for which purposes. V - agreed, we often confuse registries and databases. Alexis: for a registry to elucidate the natural history of a disease: 1. This means that it can only be per disease 2. This means that you have to know the symptoms of the disease 3. It means it will have to be updated regularly (every 3-6 months depending on the disease) and if this is

not done you will never get the natural history.

If you want a registry to show effectiveness of different therapy and management options, you'd need to have exactly the same therapeutic protocol for a given drug or a given treatment that is used by all centres. Everyone will enter what they have done but this doesn't conclude anything unless you find the very striking side effects. The easiest registries are the ones which allow us to know where the patients are and then when you have a question to ask and the budget to answer you know where to go to find the patients and the physicians that are useful.

OK. I am very interested in this but the landscape is confusing and we are stretching the definition of registry somewhat here, although I do believe that natural history studies and registries belong together and should ideally be integrated as much as the technology will allow - whilst retaining the integrity and interoperability of the core data. I believe (or at least hope) that as we develop better tools then different diseases have much to learn from each other and some breakthroughs might be delivered by aggregated registry analysis. But I am giving myself a headache just thinking about it!
I would propose that maybe it's a little different from field to field such as different communities that run different types of these. It's quite true though that if you're trying to collect natural history data, for instance, there's quite a bit of information needed to agree datasets etc right from the beginning (unless you are really mining unstructured data somehow)

To centralise a big registry is non-economic and not realistic so would be the thing to avoid because you will face the sustainability issue very quickly and new data is produced all the time. I think there are three different options: one is the unstructured data and this will help to capture natural history. The second would be of the Federated registry, so you're collecting data with a minimum data set or for a specific purpose. The third is the national registry.
I think we have more permutations and combinations than that, Ana, whilst not disagreeing with you. The problem is that the term registry is way too vague and all-encompassing and the first thing we need is some kind of consensus on the different types of registry and how they do (or could) fit together.

Important for all fields to developing meaningful minimum common data sets, and use these globally, as we did in the renal field
Absolutely and the JRC core data set is already mandatory for new ERN linked registries, or as good as. But we can have concentric circles of cores as we get closer to groups of diseases at least. Specific disease registries are likely to differ but should still incorporate the core(s) in this model.

How can we manage to integrate all small RD registries in university hospitals, patient advocacy groups, non EU states like Switzerland into the ERN RD registries to get one really big registry for many of RDs? Maybe the ePAGs could contribute in their field to collect the information where these small registries exist and share the information with their ERN or registry coordinator

Agree with Ruth's point (immediately above). If ERNs are the answer (I believe they are) we have to recognise that, for the time being at least, ERNs are by definition elitist and limited in coverage. We need to find ways to make the registry aspect of ERNs work more inclusive whilst at the same time maintaining standards and data quality. An ERN registry containing only ERN members' patients is a nonsense.

FAIR is not the answer, or at least not by any means all of it. I hear this repeated as a mantra by people who fail to understand the complexities of registry operation. I would also add a further R (FAIRR?) and believe that **Relevance** is a crucial aspect that is not reflected in FAIR. Relevance in terms of what we are collecting and how we are using it as well as permeating every aspect of registry creation and operation.
I fully agree with this comment. FAIR principles is an evolution of a new way of data standardization, which are readable between machines (computers) but registries are more than FAIR, because they require governance, procedures and quality, among some others questions.

In stressing Relevance (point immediately above) of course we need to understand that rel**evance** is rel**ative** -

what is relevant for one person may not be to another. In order to solve this conundrum we have to **compromise** - but how do you compromise on something as important as healthcare? The answer is that when looking to compromise we must always ask what is in the best interest of the patient? That doesn't solve every problem but if we all have that objective it does make things easier.
In a perfect world I want one registry for each rare disease covering at least the whole of Europe. Is 7,000+ registries feasible? Maybe not under current definitions but we have the potential now to create virtual registries and if we are to leave no patient behind in treatment then that phrase becomes nonsense if we don't understand their disease in the first place. In many situations, grouping RD registries based on either their clinical relationships or their pathways connections are also useful and it will limit to split RD registries in thousands of them (ie: metabolic or neuromuscular diseases, etc). However, in some cases the specificity of some RD requirements will create the necessity to organize a registry for one RD only.
Linking a couple of the points here with Russell's above: registries developed with patient and carer involvement in the design, and direct data obtainment, *if built explicitly around data security and interoperability* - there's no reason in principle why that isn't scalable across all rare disease without loss of generality. The main challenge is likely to be the datasets, but a core common dataset with disease specific modules is hardly new - QLQ-C30 and FACT modules, for example, are good examples within the PROMs world.
Data nowadays are existing in some form of a technology database. How do we access them so that we can eventually pull all those data from different registries in different regions in different languages, all together?
We should look at bodies like ICHOM. International Consortium on health outcome measures. There are outcome sets being developed for several rare diseases now, I think these will be a good starting point to see how we can involve patients and clinicians in the data capture and to give the data back to the patients via dashboards to discuss them with the doctor during the consultation. I think that's important to use the data in the management of the disease. I'm interested in seeing how we can link personal health records. this is a system that is being developed in the Netherlands where I live right now where patients can contribute their own data and measurements of their own things like that but I was hoping also to use this system to capture the patient reported outcomes and surveys I think these will be success factors for registries, if we can link, for instance, personal health records to registries that would be great.
The biggest failure rate in registries that I've seen is legacy. They are started but have no provision in either consent or design on how the data will survive beyond the life of the group that starts the registry. We have been working with that issue on the https://rarediseases.org/for-patient-organizations/ways-partner/patient-registries/nord-fda/ program where the registry reverts to NORD if the patient organization goes away and can be vested into a new group. Has to be included in the original design. *Sure. Sustainability is key but hopefully the ERN element of registry structures should prove sustainable (as long as the ERN itself is sustainable) and that already provides a solid foundation for a disease registry to build upon. If we get a systematic roll-out of a proven model then I believe sustainability issues will be reduced - not eliminated, but much improved.*
It would be nice to see if we can look at cross sharing structure ontologies/organization/standards internationally. Given the amounts of resource spent in US/Japan/EU/elsewhere it would be good to borrow/steal/use what exists. Peter: There is a lot of work going on at the moment to try to bring various standards of organisations together and a lot of this is being fuelled by the need to move to a learning health system to create the exchange of information from research into healthcare and from healthcare back, and that means things like HL7 and FHIR, and they have to be ISO. We're working with CDISC and we're coming at this from a genomics perspective.
The role of Patient Entered/Generated data would also be good. We are finding it unsustainable to have registries for the many disease and patients with physician/staff entered data. Patient entered data has some

good validation (if done properly) and significantly reduce the cost of a program.
Blockchain has a few problems in that the origin source of the data (such as a hospital electronic record) can have access blocked. This can happen over time with rule/firewall/EMR changes. Would suggest instead that data be pulled into registry and secure data key be provided for access to appropriate individuals. We are also looking at giving the patients access to their own record (with a data key that they can share if they want).
We need agreed clinical and patient reported outcomes by condition. Then we need the research projects ($$). Then work backward to identify optimum data set. When researchers are ready, approach the patients to complete the missing data. No point in populating a registry unless it's going to be used.
A useful resource to follow is the Personal Health Train. This is being developed based upon the need for accurate health data. Many actors will be involved: Doctors (HCPs), Patients, Government, policy makers https://www.dtls.nl/fair-data/personal-health-train/
Registries are not always designed ideally. In Hemophilia, World Federation presented the global registry in 2018 and so far several countries have started populating it with patient data. The registry is heavy and cannot be linked with other registries for automatic data uploads. The global ID and data security still is a question. Local ethical approvals as hurdle.
What is mostly needed in order to really make RD data interoperable/linkable is 1) the joint effort to use the EU RD Platform as the central access point for information about RD registries and their data, which translates in encouraging all existing RD registries to join the EU RD Platform; 2) avoiding initiatives that duplicate or partially overlap with the EU RD Platform and diminishing the convergence of the RD registries to this central platform. *Like I keep saying, ERNs are the answer! :-) I think it inconceivable that an ERN managed registry going forward will not adhere to the JRC guidelines and contribute to the registry of registries. As a patient I would like to see all existing rare disease registries migrated towards compatibility with this model and all new RD registries to be constructed with this uppermost in mind. No need to make it mandatory -if funding opportunities show a clear preference for this model and the ease of interoperability that will surely follow and are demonstrated then everyone will want to join the club.*
Another missing piece is a serious effort to overcome policy and funding fragmentation across the EU and misalignment with national initiatives. And this affects the health sector overall, not just the rare disease field. Too many activities, projects and initiatives at different levels but little opportunities for scalability and poor alignment between all these different activities. We need to break down silos to overcome funding fragmentation and favour cross-disciplinary, cross--sectoral innovation. We might not need a Horizon Europe mission for a European health data ecosystem, but we certainly need concerted policy action in this field.
Beyond the technical aspects linked to standardisation and normalisation of data, another missing element to open up data is to change the incentives structure around data sharing. Once we have achieved to clean and normalise the datasets and solve the linkage problems, we need in place the adequate incentives to open up that data. Todays' incentives do not favour data sharing.

Annex 3: Policy Consultation with the Panel of Experts on Topic 3 (Availability and Accessibility of Orphan Medical Products and Medical Devices)

a) How can we stimulate greater development and access to medical devices for people with rare diseases?

Comment/Response
Simplifying clinical trials (while respecting patient safety) especially for devices. Less constraints and the possibility of involving more patients. Immediate reporting of results and benefits in general.
Concerning medical devices: I think we should start a conversation with DG RTD because one of the tools available are the fast track opportunity – it's a call that takes place every 3 months for SMEs and they can propose a project. We could take advantage of this
On the devices side, of course, we have the new(ish!) Regulation on devices from a couple of years ago. And that was an improvement. Most agree there are benefits to this Regulation e.g. the greater emphasis on actually having more substantial clinical evidence around the device and not just looking at the safety and the risk benefit ratio. But there's still a lack of transparency around the process of notified bodies doing their clinical evaluation assessments. Also, there is the fact that in most countries the actual bodies who oversee the process of assessing pharmaceuticals and devices are separate in most cases. Our KBS mentions the US example, the humanitarian use device exemption: does anyone have any insights on how that came to being and how effective that is in the US in terms of having specific incentives for devices intended for *orphan* use as opposed to the general population?
There are particular benefits to having better (and earlier) patient involvement in Medical Devices development: I think in a world where hopefully we are more and more aware of the benefits and the need to involve patients in the design and creation of different devices, the ERNs could act as quite a nice centralizing force.
I wanted to recall a little bit of what has happened for the medical devices part. It has always been difficult to tackle and I remember we (Eurordis) entered into a type of impasse in the sense we were asked exactly what was the problem for medical devices intended for the use of rare diseases. We entered into discussions with the European level organisation of producers of medical devices and we as both the patient movement and the producers discussed what exactly we were trying to tackle. We were told at the time there was no problem with the production of any sort of medical device for a specific patient, for instance, for a patient who is allergic to titanium anything can be produced and we thought about the humanitarian use of medical devices for rare diseases which basically grants the producer the exemption of having to demonstrate effectiveness and we were asked to consider whether this was really the most useful way

forward in the sense that not having to demonstrate the effectiveness is a double edge and the ***actual real problem was not the production, not the approval not the level the evidence but the reimbursement phase***. I don't know how we can potentially overcome that but in the absence of a centralised authorisation of the devices themselves, there is not a lot the European level can do. It really depends on the priority that health care will give to medical devices.
ERNs can add particular value to Medical Devices Development : *As someone who when it comes to almost any question in the rare disease world feels the answer is with the ERNs I might be thought to applaud this but actually what worries me is that the ERNs are already being asked to do far too much and in two or three years time I think they could be a great vehicle for improving the world of medical devices, but in the meantime they are under resourced, over burdened and in danger of collapse if we try and push too much on to them in the short term.* I think that the ERNs can work on this because medical devices are relevant for some ERN but there are other ERN in which medical devices are not so relevant. One simple way to get some information is to provide a call in order to run this kind of evaluation of what is already ongoing in which specific field and what are the needs of the patients and what are the ideas and tools that are being pre-developed and could provide a step forward in this kind of situation. By putting in a limited amount of money (ERN couldn't manage with the current money), they could run this kind of business because we already have the networks to collect this information but we need the resources.
The medical devices new regulation might offer new opportunity, especially in rare diseases. But there's also quite a big risk involved in this whole regulation because all the devices which have been registered have a temporary license and need to be renewed every 5 years. Whenever they have to be renewed now after the device regulation comes into force, they need to comply with the new requirements. This means that some of them, which have never gone through medical trial testing, should have medical data, which are not there yet, or has never been systematically collected. That might also mean risk. I also think that medical devices are used off label- not sure within new regulations if that will be possible or continuously possible
When we define significant benefit at the time of *drug* authorisation and evaluate value at the time of orphan reimbursement, there often comes a point where we ask for things like managed entry agreements which require ongoing data collection. But there is a data silo between the medical device directive and orphan drugs follow up data. Ideally, I'd like to find a way to ensure that any medical devices that have been used in conjunction with orphan drugs have a more harmonised data collection plan. I sometimes find it frustrating that these different data generation requirements or follow up requirements are not so well aligned in terms of how they're done and conducted. I understand that they're often asking slightly different questions but a more harmonised way of collecting this data would be valuable for regulators, notified bodies and HTA assessors
I'm not very familiar with how the medical devices work now, but my feeling is that they should not be evaluated towards disease/disease area, but functional need of the patient. Lets say if person with pulmonary arterial hypertension needs oxygen device and tools to measure its saturation, only a small part of evaluation should touch this particular disease, keeping in mind that also other diseases might need the same equipment. Same goes to mobility devices. And there should be pan-EU catalogue of approved and recommended devices for patients and specialists to search trough, and for small countries like Latvia to quickly navigate the selection of what and how other countries are providing to whom, on what conditions. Something like a tripadvisor, because now patients and patient organizations do this evaluation in small groups, forums, then each of us tries to get them personally or into national systems, and the effort is every time the same. I believe IT tools can help handling it better already and definitely in future.
Echoing Baiba's comment above; a workstream I lead with MIT NEWDIGS is on 'patient and caregiver perspectives' - one of our big findings from that work was a clearly articulated frustration with the fracturedness of the US system and a need for a 'research navigator'. We tend to describe that as, "a travel agent for financing options." This is analogous and I think the idea of an aggregated site of knowledge of devices, evidence behind them, and then a 'travel agent' for patients, carers, and providers, will help bring all of that together. Once

cohered, this can also help to become the basis of energy for advocacy and policy development - again echoing Baiba's point, this would be a single push at the idea of medical devices for rare and orphan diseases - as opposed to currently, where that energy can also be disease-specific and fractured.

b) Is the current legislation concerning OMP access fit for purpose? Where could improvements be made?

Comment/Response
Considering the complexity of rare diseases, I think that the authorization of drugs (EMA) should be more flexible even with little but good evidence, perhaps dividing the authorization into 3 levels (low-medium-high) and monitor over time the effectiveness on an annual basis. Given the existence of compassionate and off-label use. (this to my knowledge of the legislation)
Equating paediatric and adult for chronic diseases.
New technologies and devices could reduce costs of hospital examinations and maintain a high quality service and patient monitoring.
Orphan Drug legislation has been a game-changer in many respects and was much needed. We have to accept, however, that some changes have been less desirable, even if inevitable. Chief among these has been the contribution of orphan drugs to the **worrying trend towards higher drug costs and the risk of a backlash from the HTA community especially.** There are growing calls for the orphan drug legislation to be refined, amended and even in some quarters for it to be cancelled altogether. Such calls are likely to be difficult to resist and we should IMHO **embrace them and work with those calling for change**, rather than engage in futile resistance. Given the imbalance between those treatments that are approved and those that are reimbursed this is actually urgently needed by rare disease patients as well. Even the existing legislation can be made to work better than it currently does, however. Some protections exist but are rarely used.
I think there are some initiatives that are active to simplify this methodology. **Last year at EMA there was an initiative with the stakeholder forum in order to collect information and proposals from all the different stakeholders for the new rare disease legislation that should come out in next year. In October there will be a European network paediatric meeting which will be a good opportunity to discuss this.** **Regarding paediatric regulations, one of the most relevant points is to make the IP(?) simpler and more direct because it's quite complex, especially for academic institutions. One of my suggestions is to have a sort of help desk that could provide this kind of information more specifically for the rare disorders.**
Rare disease Registers with ontology codification could encourage the development of new study/research and/or use of transversal drugs (authorised for other disease).
If you look at the KBS section on numbers of OMPs for certain therapeutic areas, there are many conditions which really have nothing in the designation pipeline. *I wanted to comment on the frequency and we need to make sure we target the right diseases. Also if I'm correct not all the rare diseases are* amenable *to treatment so we need to look at the full picture and when we talk about 6000 or 7000 diseases I think in there there's a lot of malformation syndromes, or things where it's more about prevention. It is likely that not all are a target for medicine development, so this is also an element that's important*

to keep in mind. All patients deserve of course the right track into the healthcare system and social services. So in terms of rare disease policies it makes total sense to look to the whole picture

Cost of OMPs: There is a myth that all OMPs are hugely expensive and overpriced - in reality, the stats show a large percentage of them are 'reasonably' priced compared to medicines for non rare indications. So sometimes there are incorrect assumptions

In my experience, almost all of them are overpriced, quite honestly. I've spoken to a number of companies and the supposition is the base price for an orphan medication is about 100,000. Anyone charging less than 100,000 starts to question themselves and say, well, this is not the price for an orphan medication.

100,000 is still a lot of money for a repurposed out of patent medicine which still forms quite a lot of rare disease medication. I'm not really targeting the half million drugs because those figures can be easily justified. It's actually the ones that come under the radar that very often are overpriced and are priced at a level that is out of proportion to the benefit they deliver to patients.

The fact that legislation can be abused by several companies is not surprising. When it comes to the very rare diseases, we've got to wake up and recognise that is never going to be corrected through a pricing mechanism. If you've got a disease that has a dozen patients throughout Europe, we are never ever going to be able to incentivize a company to invest in research through pricing. There are two ways that we can do it: one will have to be from the public purse. We have to fund it in our institutions or subsidise it for industry. The other really is to find the reasons why companies who develop a treatment for a rare disease can learn much more about the treatment and the mechanism and use for a more common disease, which would then be the money spinner. So it becomes a loss leader, if you like, but rare disease drug pricing will never help people with very rare diseases.

Sometimes I think people focus too much on the 'abuses' from Companies - the irritations stem from a small number of cases or a number of things that will not happen again so I think the focus should really be on the rare diseases and having investments or better collaboration around those fields and we should be careful not to **over**compensate.

And there is also something that has happened since the legislation has been in place with incentives and HTA has really improved. There is now a good bridge between the regulatory access, the willingness to invest more in rare, and how the HTA bodies handle this. We need to make sure we continue to focus on the most complex diseases, the paediatric cases where it's quite difficult to have investments: we need to find a consensus to handle those cases.

No: the current legislation does not work well enough. We have been aware of the main cause of the failures for a long time, and it is getting worse: the issue is that this Regulation in Europe was based on the US regulation, in a liberal environment in order to incentivise investment to create a market where there was no market. So it's an economic liberal regulation and that works well for the US and it kind of works well for Europe in terms of attracting investment. But in terms of market, it doesn't work. We're acting as a follow up market of the US market because the fact that we create an incentive to attract investment of market exclusivity, yes it does create attraction. We see from the designation and from some companies that started in Europe and some developments made in Europe that this works. . There was also additional incentives on tax credits and other public funding, so this is very positive. However, when it comes downstream after the marketing position, the discrepancies of evaluation on the effectiveness and discussions on price and reimbursement take place and finally at national level and sometimes local/hospital level doesn't work for that type of product. A major difference is that all these products are being paid in Europe by public money, not by private insurance companies. It's public money for all type of people in Europe, whatever the revenues we have, so we need to find a way to regulate economically, the relationship between public buyers and the companies developing this product. Many organisations are pushing to European discussion on pricing. Everybody says this is not realistic but this is the thing to push. It's nonsense to do what we're doing, negotiating access for patients, long

differences of delays across counties and this will be worsening with the gene therapies.

Does the registration pitfall propose? No it doesn't because it only addresses investment, doesn't even address research really, much more could be done to stimulate research for diseases where there is not enough. We need better preparation, better dialogue between stakeholders. We have a clear lack of continuum and lack of collaboration between the HTA and the peers and we need European collaboration, regulation can do that.

A lot to discuss here and I agree with most of it in broad terms but would like to comment on some specifics.

Harmonisation of pricing on a European level is an obvious goal but it is a long term one, I am afraid. It will be possible and, indeed, desirable for small collaborations to grow and for others to join them but we have way too much economic and political diversity in the EU for this to work on a grand scale. Think about it - if we went the "Whole hog" the pricing and reimbursement authority would effectively dictate a large chunk of the health budget in individual member states and most of them would not contemplate that.

There are workarounds but too complex to discuss here - a community-wide insurance scheme would overcome many of those issues but this in itself is politically poisonous and even mentioning it could cause problems. Meanwhile, a mandatory development of EUnetHTA type collaboration on a much bigger scale would be a giant step in the right direction and, I suspect, is ambition enough for this time horizon.

As we're looking at more constraints around the health budget, even if we try to make the case that "by investing in medicinal products and innovative therapies, we're going to save in the long run" the upfront investment isn't going to be there. The time has come for a totally different paradigm. We've had orphan regulations, which have been pushed as far as possible. Not having such regulations in Canada is compelling us to think of a different way to address this business.

No question. If we were designing a healthcare continuum from the ground up it would look nothing like the model we have now. Changing that model has its attractions from a philosophical point of view, but is unlikely to be possible even to contemplate in such a turbulent economic environment. You have to spend money to save it, but nobody feels confident enough to spend, I think.

I do think the pendulum has swung too far re. incentivisation and orphan drugs. It's not sustainable in a way that will maintain public funding. It is clear that all big pharma companies are moving into orphan diseases, not because of philanthropic reasons but because it has been demonstrated that the profit margins are better for them now. So in itself, the huge shift we're seeing in big pharma companies towards orphan drugs is a clear indication that the incentivisation granted in the existing legislation is working too well, if you think in terms of profit margins. The drive to address this really needs to be government forcing pharmaceutical companies to re-examine their profit margins and embrace transparency: this is urgently needed.

It will be necessary to withdraw some of the incentives in their current format, but at the same time maintain a fairer, societally-balanced view around investments in the right diseases across all areas. Otherwise we will face huge problems moving forward.

So, you believe that the world has been too generous to rare diseases and we now have to accept less in the future? This is not a "zero-sum" game - money not spent on rare diseases is not necessarily going to be spent on other diseases it is just as, or even more likely, to be spent on other investments.
I suspect you will find very few takers in this forum for the notion that too much has gone into rare diseases and we do not live in a planned economy. When I see large sums going into a disease area that is not closely linked to those in which I am concerned, far from seeing that as inequitable I celebrate it and hope that we will get some of the crumbs from the table. Medical innovation is a very imprecise art (I hesitate to call it a science) and the history is littered with accidental discoveries when searching for one disease and stumbling across a cure for

another. Short of world revolution we have to learn to work the system we have and search for collateral benefits - powerful registries will be a massive tool to facilitate this. *Obviously the best way to accomplish transparency and fair pricing would be to centralize and couple pricing negotiations to the approval process at the EMA level, bringing to the table the market power of 500 million EU citizens rather than single countries, regions or even local institutions as practiced today*. Although Hans-Georg was understandably reluctant, I do feel that EMA likely has a role to play here, however politically delicate this might be. But as with many things, we have to be very careful not to break that which is precious to us.
With the advent of precision medicine, a lot of things are going to be classified as orphan drugs without ties to what we typically classified as rare diseases, e.g. cancer drugs targeting specific rare mutations in otherwise common cancer forms. We may move into a situation in the not to distant future where half of new medicines are categorized as orphan without this being a significant development for rare disease. This is probably not what was intended by the legislation in the first place so it will pose challenges to the health care system.

c) What practical actions (at national and European level) would increase the accessibility and availability of OMPs?

Comment/Response
In addition to authorisation, EMA should be able to define a basic political price range for medicines (minimum and maximum) in order to simplify and speed up national procedures.
It should be allowed to gather more data (efficacy and not only safety) from patients on compassionate use programs. This is forbidden by law currently?? Can bring many valuable data *The fact that the data that are generated through compassionate use cannot be used by the company is a disincentive this is a loose- loose situation because there are data out there that are generated into real world settings and it's really a pity that they cannot be integrated into the overall data set*
More collaboration in HTA assessment
Price negotiations at EU level (set a general price and than recalculate based on GDP per country)
We are setting up a committee on rare disease medicines for all. It is important to think about these issues on the global level: once we start to think about the global market, we talk about what the needs are globally and analyse access globally. No matter which country you look at, the medicines and therapies are simply not reaching the people who need them, and to make any sort of change in this area we need a major paradigm change.
There should be more information about that not all RD need OMP, but can be also treated with regular medicines (specific or wide use, cheap or expensive), otherwise now we focus mainly on very expensive and hard to access treatments, compromising other diagnoses, where treatment exists: therefore we try to help one group of patients, but at the same time create more barriers for others. And public thinks any rare disease costs millions, although there are many which are not that expensive. Governments love to use this to make patient groups compete among themselves, with other patient groups (eg cancers) - and such environment does not help to solve situation. And for OMPs, we should push more for purchasing schemes, not leaving it to each country or group of countries

(eg Latvia with its less than 2m people, 4% GDP for healthcare and 15K e/per capita GDP would never be able to ensure access to same treatments as France, Germany, UK and others. Even if we bundled up with other Baltic countries, we would not be as powerful as rich and big countries to negotiate the price, therefore there would always be delays to access. In this way we push people either to die, suffer from disease or make them move to other countries just to get treatments, or in some cases even to cheat with paperwork. Cross border health care directive is not applicable in this case, because it assists only if there is a price for treatment (medicine, procedure, anything) nationally, and this price usually is one third of what other countries pay. Even providing treatment via ERNs, would leave patient with what his country can afford (and ours mainly denies everything because of lack of money). This is not fair, we are not less worthy just because born in less fortunate country.

Annex 4: Policy Consultation with the Panel of Experts on Topic 4 (Basic, Clinical, Translational and Social Research for Rare Diseases)

a) How far have EU countries addressed the requests in the *2009 Council Recommendation on an action in the field of rare diseases* (see Knowledge Base Summary pages 1-2)

Comment/Response
The Council Recommendation mentions cross-country collaboration, especially on involving the eastern European countries. From the point of view of a funding agency, from an E-Rare and a Dutch point of view, E-Rare has done a lot to get people together, from Western and Eastern European countries. This takes a long time, but there is more interest from countries in general and from the EU13 countries, which is good. The Dutch research funding agency has used these kinds of recommendations to let the MoH know that there is more to do. There *has* been a specific programme for research on rare diseases, however the MoH is less interested in the national plan and funding research as they say it can be done in other programs.
Definitely more international cooperation in RD research now, compared to the past However, there is often no dedicated funding programme for rare disease research, in Europe or the US.
I have noted an increase in interest in rare diseases in some countries, but not from ministries in the Netherlands. Dutch researchers, clinicians and rare disease patient organisations have great interest. There is no longer an expert group where countries can come together to share experiences on adopting, implementing and revising plans and strategies. The Council recommendation asked countries to adapt their plans and strategies by the end of 2013, but there is nothing in 2019 to say that they must replace or renew them when they expire. Data collection for the state of the art resource showed that many countries do not have a separate program or funding stream specifically for rare disease research
However, social research was very difficult to use as a topic for E-Rare because funding agencies were either not interested, or it was too nation-oriented. A workshop in September will address this. A survey is also collecting information from funding agencies about the kinds of social humanities research currently being performed or has been performed in the past. It is also looking into interest in having a call on social research and social economic research in the future EJP RD. We see that more funding agencies are getting interested in social

research for rare diseases. It is a pity that it was not done in the past, but it is necessary to do it in the near future.
No clear overview available as far as I know.
Collaboration through the EJP-RD program.

b) How do we accelerate the rate of progress for basic, clinical, translational, and/or social research? (Please make comments on each individually, if appropriate, or else identify something which might address all as you wish!)

Comment/Response
Dedicated research funds for disease areas and complex conditions as described in the ERN structures
Publishing data from clinical trials that do not succeed to inform future research. Placebo data is often also siloed. The OECD report will be very valuable Similarly, we need additional incentives to publish negative (also called “null) results from preclinical and basic research studies in order to advance and avoid wasting of funding
One problem in many types of research are the very bureaucratic ethical committee processes and similarly complicated processes relating to data protection. If these could be more flexible, that might help. Especially in “small” projects like collecting natural history for a very rare disease, these permissions may be the biggest part of the workload. Again, something that patient organisations could take into discussion: flexibility, no paternalistic over-protection
The ERN recently published a paper regarding the actualities and potentialities of the ERN. It is evident that ERNs are not only clinical networks but they are a good fit for research too. It is not only a matter of funds, but also a matter of organising the infrastructures present, and the knowledge of the different tools available. Very few people knew that existing infrastructures are available. The ERN coordinators group think this is a major topic for consideration. Now is the time for countries to review and redo their national plans for rare diseases, not only to raise funds for research but also to better use what we have already.
Need to listen better to what the patients really need and to try to encourage basic research. There are many therapies available in the metabolic field, but there is a need for basic research to understand how these therapies could work. There is a need to encourage the ERNs to make more basic research and to understand how the therapy should be developed, together with implementing artificial intelligence. A lot of data cannot be

analysed. There is not enough machine time to compare big data banks that can generate a lot of ideas and resources for research.

We need calls specifically targeting collaboration between ERNs. The (??) Call looks at facilities across the ERNs, such as bio-banking, exchanging materials, registries. If we can easily exchange materials and data, this would facilitate more research in the ERNs

We do not see a quick enough reaction to the reproducibility crisis, especially now that we are trying to pull more and more data. We still see that the data might be 50% to 80% non-reproducible.

Pooling data, using machine learning and AI trained on data may be spurious and we may end up throwing away many resources. We need to concentrate efforts on trying to bring more attention to reproducibility at all stages of research. The work done in the EJP will only go part of the way, as there is not much work being done to look at the laboratory process. The funder and the publisher are the gatekeepers who can actually force the change. We have to work as a community to look at how we can bring rigour to that process. This includes looking at the funding process itself. To help the funder work with the researchers as an investor in the research and try to help to give them access to the resources, the expertise, the tools that are available in places like the infrastructures and the ERNs. We need to help design robust studies, before the actual funding happens.

A lot of funding is now coming through patient-led initiatives. This is good, but it is fragmented and they have little resources. They often need guidance on how to spend the money on something other than some small, basic research studies. Greater coordination and collaboration between funding sources would be good, even across sectors, for example, charities working with public funders or public funders working with industry on precompetitive research

It would be helpful to know how many projects that funded so far actually went to a real therapy. This can direct the researcher towards something that can be useful and make a breakthrough. We can organise this inside the ERNs. Give a critical reading of research done so far

The Immunological ERN feels that it is important to have strong ties with the learned societies, as there is a lot of research done and there is a big overlap with rare diseases.

Many more centres could contribute patients to activities led by the ERN or the learned societies.

Need to try to work together to create a big "push" around repurposing. Everyone sees the benefit, the potential and the need, but no one really knows how to do it on a big scale. IRDiRC is setting up a taskforce to look into this

T*he ERN Coordinators talked about repurposing at the conference in Brussels last November. The talked about whether the ERNs can play a key role in repurposing of medicines for rare diseases.*

For repurposing - Matt Might is a prominent rare disease researcher and advocate to pay attention to in repurposing. He has the "mediKanren" tool. https://www.uab.edu/news/research/item/10382-a-high-speed-dr-house-for-medical-breakthroughs

Translational research still needs more registries for disease knowledge (e.g. natural history), stratification of patients, etc.

The EMA has just put out a regulatory science strategy for 2025 that was up for public comment until the end of last month. There is some language about rare diseases and orphan drugs in there.

Ten years ago, there was a big push for repurposing but it came to nothing. If there is investment in repurposing, does anyone know of an example of when this has been successful?

Can think of only a handful of cases where repurposing has worked well. One assumption a number of years ago was that it would be easy and cost nothing. It is not a light option however, because you still need to do proper studies.

We can gather some examples, and this could be a useful piece of work under this part of the project, probably in close collaboration with some of the ERNs.

The STAMP expert group has also been focusing quite a lot on repurposing in recent months

Nico: Has an example of a very successful repurposing but that was because it was an expensive drug so the pharma companies were interested in increasing the market. The drug was previously dead, until there was new insight on the pathogenesis of some disorders. It was not cheap, as phase two and phase three are necessary. There must be an incentive for the company, such as a high price for the drug.

Agree: The problem with repurposing is how to protect IP for the developer. The Congress just introduced the 21st Century Cures Act that provides further incentives than the Orphan Drug Act. Need to think about how to encourage the pharma companies to invest. It is not cheap, as most expenses are at the phase two or phase three level.

Devices: The incentive issue is also one of the main points about medical devices. Again, this is a good area for ERNs to become involved. There are a broad range, but medical devices and aids for many conditions still do not have any sort of disease modifying treatment and will not for a long time. It is important to do anything possible to make life a little better and prevent symptoms from getting worse. There are the same issues around high cost and access, and there is potentially limited incentive for companies to get involved, as there is no equivalent of the orphan drug legislation for devices.

In 2010 an analysis of Orphanet (RD Platform) identified 3 determinants for accelerating research in RDs: existence of patient organisations, existence of ERN or clinical network and existence of a registry. More information here: https://www.eurordis.org/content/building-rare-disease-research-europe and here: http://download2.eurordis.org/documents/pdf/1_%20ayme_RDD2010.pdf

Agree with Wout that there should be dedicated research funds in EU framework programmes for research into specific rare disease areas as defined by the ERN structures.

A general comment: For the development of RD research themes for EU funding, instead of the traditional top-down approach it would be important to go bottom-up, starting by surveying (ERN) clinicians and patient community to assess the most pressing research needs, then prioritizing topics by cross-checking feasibility with expert researchers and ending up with disease-group specific research themes prioritized by urgency-feasibility analysis. With this approach research projects would be much better anchored in, and supported by, the clinical community.

It would be helpful to align the clinical research goals with the new clinical trial regulation that states for example

'Member States should efficiently assess all clinical trials applications within the given timelines. A rapid yet in-depth assessment is of particular importance for clinical trials concerning medical conditions which are severely

debilitating and/or life threatening and for which therapeutic options are limited or non-existent, as in the case of rare and ultra-rare diseases' Clinical trials for the development of orphan medicinal products as defined in Regulation (EC) No 141/2000 of the European Parliament and of the Council (1) and of medicinal products addressed to subjects affected by severe, debilitating and often life-threatening diseases affecting no more than one person in 50 000 in the Union (ultra-rare diseases) should be fostered

c) What would be a 'game-changer' for rare disease research?

Comment/Response
Dedicated data managers mining current clinical files and data input in the new ERN registries
Dedicated disease area specific PhD researchers for the expertise teams (900) within the ERN HCP's
Many developed countries do not get the required support from their governments. Developing new diagnostics and treatments for rare disorders as well as performing epidemiological research on those disorders, requires multi-country approaches. This should include other nations such as India and China as there are more patients there than anywhere. This is a great resource for clinical trials and diagnosis of undiagnosed diseases. *Multi-country approaches would require promotion of Orpha codes in the healthcare systems. This would help with finding patients for research. ERNs should be actively helping Orphanet in developing and updating the Orpha codes*
We need to concentrate efforts on trying to bring more attention to reproducibility at all stages of research. Broader mechanisms for data sharing (whether directly from the patients and families streamlined from the clinic into research, or otherwise) is a game-changer in realising the potential of machine learning to benefit rare disease researcher. Smaller sample sizes make a lot of powerful approaches impossible otherwise.
It would be great to see a **regulatory science agenda set up and financed**. Many advanced therapies are going to have a use in the rare disease field. As these emerging technologies come towards regulatory processes, there are many open questions. Being able to answer those as quickly as possible would help ease the regulatory burden and be very valuable.
• open access to research publications • More efficient public spending in support of rare disease R&D • the requirement for all authors submitting research papers to include a "Patient and Public Involvement Statement" within the methods section of their paper describing how they involved patients and the public in their research… as per BMJ patient partnership strategy

The use of the European Platform on Rare Disease Registration (EU RD Platform) developed by the European Commission is a game-changer for rare disease research. The Platform is conceived as a central access space for all existing rare disease registries with their characteristics and metadata. Based on the Platform's components: European Rare Disease Registry Infrastructure (ERDRI) composed of the European Directory of Registries (ERDRI.dor), Central Metadata Repository (ERDRI.mdr), EUPID pseudonymisation, search broker and data warehouse, the Platform will make registries' data searchable and findable thus reaching the critical number of patients needed for all types of studies and research.

Annex 5: Policy Consultation with the Panel of Experts on Topic 5 (Diagnostics)

a) What barriers exist today to receiving an accurate diagnosis?

Comment/Response
The KBS highlights the Voice of 12000 patients study performed a decade ago, led by EURORDIS. Have things improved dramatically in terms of diagnostics, since this study was performed? Perhaps in some regions of the world more than others. EURORDIS will likely be updating the survey in the next few semesters, and it will be very interesting to compare and be able to answer that question much more accurately. One of the most striking things from that survey was how effective simple awareness raising could be: one of the major factors leading to a faster diagnosis was simple recognition that a generalist or a specialist might need to 'think outside of the box'. So awareness raising pure and simple remains a major priority, to overcome the barriers. The fact that the situation might have improved in some Member States and in some regions of the world yet not in others means there are probably greater disparities between countries today.
The KBS document shows the 'RD Pyramid' from Orphanet. One barrier is surely the speed and efficiency of that patient journey from General Practitioner to reaching an appropriate Centre of Expertise. The importance of the CE role for enabling a prompt and accurate diagnosis is absolute: CEs have a sufficiently high volume of referrals, even for very rare diseases, to allow experienced clinicians to almost diagnose patients with very rare conditions simply on sight, at times. If we can get patients to the Centres of Expertise for their disease then their chances of getting a diagnosis are much better – the inability to do this smoothly is a major barrier
NGS is not a generalized service Please let us be careful focusing on this without moderating our request. It is part of the standard diagnosis procedure and that should not initiate the procedure because we have more and more results that are "non conclusive"
Lack of common standard diagnosis procedures for rare diseases diagnosis
Lack of structured data from patients *(And also from care providers and researchers)*

Awareness in primary care e.g. red flags for rare diseases *(And also in "secondary care" (outside centres of expertise/excellence/reference) not as often as in primary care but this lack of awareness does exist and needs to be tackle* *Some ERNs (e.g. ERN-RND) have mentioned the key issue of getting patients referred to centres of expertise in the first place* (Yes, and also in the healthcare system itself; it is easy for patients to "fall through the cracks"; if someone bounces between >X specialists, they could be flagged for integrated/RD/genetics review)
Rare and Undiagnosed Diseases referral and care pathways are often not embedded in primary care
Insufficient investment in and development of clinical (phenotypic) interfaces, compared to investment in the genomic side of the genotype-phenotype equation Rima Nabbout: And this will increase in the coming years as we can see still a quick increase in the Molecular biology, decrease in price (and very large investments in some countries) parallel to a decrease in experts and investment in "clinical" interface. WE should keep on this balance!
Lack of culturally aware and appropriate genomic and rare disease service delivery for e.g. Indigenous populations
Lack of awareness or knowledge from national (health) authority(ies) of the existing undiagnosed rare disease patients - its number, impact on an economic level but also on the quality of and access to health and social care
Insufficient sharing of case summaries (phenotype and genotype) between institutions and internationally in order to identify similar patients and understand the spectrum of a particular disorder, because any given specialist or even centre of excellence will not necessarily be familiar with a given RD
The high cost and burden to patients of visiting the specialists necessary for a diagnosis
In our country, a challenge is getting to the right doctor who has experience in rare diseases (and in the specific one you need diagnosis in). Another problem is that genetic testing and diagnosis is not refunded by the government. Since March 2019 there is a refund on genetic testing provision, but since it was not calculated as it should be there is now a lack of financial and human resources in the genetic engineering department where testing is done. A lot of our patients go to Bulgaria, Serbia, Greece and further to get diagnosis and management advice for the rare disease, and they do this at their own expense. I agree that if primary health providers have more knowledge and resources, this would facilitate early diagnosis.

There is an issue still, it seems, with misdiagnosis and 'false alerts'. The international recommendations of 2016, produced by patient organisations in Europe, North America, Australia, and Japan (referenced on the KBS) all strongly emphasize avoiding unnecessary waiting times and issues for patients and families waiting for things. Diagnostic procedures must be as reliable as possible as misdiagnoses can have serious ramifications
It is important to emphasize that obtaining a timely diagnosis and relevant information about one's genome is a human right. Whether a genetic diagnosis is offered is often connected to the presence of medical treatment. But diagnosis should not be based on quality of life parameters or whether the condition is actionable: it could be to allow people to make reproductive decisions, for instance. Only the patient or parent should decide whether the diagnosis may be meaningful. This principle may also have consequences for the kind of diseases that are included in the neonatal screening programmes or other early genetic screening.
Several barriers still exist. Medicine is moving to AI era but for rare conditions and variant symptoms these kinds of services will not be introduced easily in the near future.
Lack of diagnostic standardization for genomic diagnostics in most of the service providers is a problem
Lack of genomic variation data (reference genome) for most of the countries/populations is still a big burden for genomic interpretation and molecular diagnostics. Lack of standardization of clinical interpretation for phenotypic findings are still barrier
Consumer production is a major issue in countries like Turkey. There's no clear regulation for the tests that can be purchased from abroad. The companies are selling these and the people are sending their material and at the end they're not receiving a diagnosis. However, in return these companies are obtaining the population data and making money. Geneticists are not obtaining the results or the population data they need.
Integrated-multidisciplinary diagnostic approach still is not in the medical practice. Medical branches and medical education still have organ based disciplines and education
Small countries, especially those with lower incomes, face particular challenges because of the low number of people suffering from rare diseases, making it difficult to set up expert centres for individual diseases, and because of lack of investment in diagnostics and organization of appropriate multidisciplinary care.
Another problem is the neonatal screening. In Macedonia we do not expect to have this for all rare diseases but having only partial screening for PKU leads to children being diagnosed when they are 2 years old which is devastating.
The still growing difficulty to publish negative results as often refused by major and even major journals
Sharing phenotype data as they are scarce in the literature and often partially published. Promote phenotype data collection (new methodologies/data mining….). Promote less expensive fees for open access journals

b) What practical actions could address the European heterogeneity and resulting inequalities around diagnosis? Are there any topics which warrant new or updated warrant EU-level (or other supranational level) guidance, for instance? How might we improve diagnostics for rare diseases?

Comment/Response
Databases managed by patients (or patients organizations)
Data donor implementation
European Digital Identity
One thing which will facilitate that journey from a general practitioner to a specialist is a system to support diagnosis for rare conditions. It is difficult for GPs because they will encounter many patients with the same symptoms in common, but only a few will need to be referred to a specialist. Appropriate triage is essential and IT-based tools and prompts could help with this. Adoption and actual implementation of those tools will be very critical. It will be difficult though, as GPs all use their own systems, and these are very different: so any solutions would need to be compatible with many software systems. *The Global Commission to end the diagnostic odyssey for children with a rare disease is a multi-disciplinary enterprise set-up last year, co-chaired by Takeda, EURORDIS and Microsoft Health Services. Launched a three pilot proof of concept projects that focus on children and bringing diagnoses to children. One of these is collaboration tools for intelligent triage, so following this work will be very important.*
It is important to find a way to further encourage any generalist practitioners to refer more readily when they cannot understand or they can't diagnose a patient. There is a need to continue to reinforce the message that it is okay for generalists not to understand everything about all conditions, to remove the stigma and encourage professionals who don't know to say 'I don't know' and find someone who might.
We should make sure that the CEGRD Recommendations on Cross-Border Genetic Testing are fully implemented, everywhere. They contain robust policies, which countries should take note of and seek to embed (e.g. the recommendation to publicize information on which genetic tests are available where). It is also important that where tests are not available for many conditions in a given country, patients are able to obtain these on a cross-border basis through seamless travel of biomaterials (and that such procedures are reimbursed). It's easier for a patient to argue to have a sample sent on a cross border basis if the country doesn't have the test for their condition at that particular time. Much easier to do that if you have a clear, transparent, open list in your country of what diseases, tests, they have. Things are changing for a lot of the countries as

move towards future of Exon sequencing or whole genome sequencing being your frontline healthcare, but that's still quite a long way off.
With ERNs to cooperate and share resources in diagnosis For undiagnosed patients to have some kind of EU doctor groups that gather to think and solve this kind of problems. it should be for different kinds of specialties.
I think it is important to highlight the role of Orphanet both in definition and in inventorying of rare diseases, since using Orphanet pages we are able to find expert clinical and laboratory centres and other relevant information relatively quickly. It will be a great loss if this portal cannot be maintained after the ONW project.
There was a particular interest and discussion a few years ago on the role that ERNs could play in facilitating a diagnosis for patients who didn't have one, or for getting a correct diagnosis for patients who may have been misdiagnosed. Before the Clinical Patient Management System (CPMS), people sometimes talked about diagnostics purely being done through that. However I think it's fair to say that most ERNs will be looking at more collaborative, international, and more fit-for-purpose established platforms to do interpretations, variant calling, case matching etc. Nonetheless, the CPMS may be useful there in terms of guiding people in the right direction in terms of how to pursue a diagnosis for their patient. *Rima: In ERN EpiCARE, the message is that we cannot think about care without also thinking about how to improve the diagnosis pathway. For our virtual consultations on epilepsy patients, with the non-surgical cases we try to give a possibility to send samples for testing; however, this will be less than 1% of cases. However, we are trying to determine the best pathways for this, bearing in mind that many of our patients can also profit from some targeted research projects that can result in a diagnosis.*
I suppose an advantage of projects like the Solve-RD initiative having strong ERN engagement (Solve-RD involves a few ERNs directly but more ERNs indirectly, apparently) is that the ERNs will surely become logical conduits for complicated and undiagnosed cases. Such patients will likely end up visiting (virtually or physically) the HCPs involved in your Network. Therefore, ERNs are a great way to catch patients who need a diagnosis and channel their cases into this globally co-ordinated diagnostic and research pipeline. When people capture their data in a certain way, it becomes much easier to pool this, even though multiple databases and platforms for this sort of genetic diagnosis exist: they can 'speak' to each other, providing the data inputters are using the same ontologies for the same sorts of data (e.g. HPO for phenotypic data). So as many of these sub-groups have said, a broader and better use of agreed ontologies should have a strong impact on diagnostics (and also facilitate extraction and mining electronic health records and other forms of real-world data).
ERNs are a good idea, but I feel that many patients will still stay outside the loop because many institutions and even countries are not adequately included in the network.

We need a particular approach for undiagnosed patients in Europe. Solve-RD is developing a Community Engagement Task Force, to think about how to address the needs of the undiagnosed rare disease population and also try to help and support genetic counsellors around the time of genetic counselling but also after. The goal is to really address the needs of the whole population (meaning the people who will have an answer, maybe through Solve-RD or other means of trying to get diagnosed, but also people who will remain undiagnosed for a period of time). There has also been talk of a shared registry for undiagnosed patients, because otherwise, how do you follow up these patients as knowledge in the field moves forwards? Furthermore, how do you capture the progression of symptoms for people who are undiagnosed? RD-CODE (WP5) is also considering how to code the undiagnosed patients better. It is likely that the people with a RD who are undiagnosed will decrease as we make more use of the technology and start to share data more easily between us: but there will always be patients who remain undiagnosed, perhaps for longer than they should.

Vicki: Agreed, there is a need to code these patients in such a way in which their cases can be easily reassessed by somebody at regular intervals, and in a systematic way. Otherwise they will fall down the cracks

Virginie: And without this, we cannot accurately evaluate the actual burden of the undiagnosed community within any given country. If you cannot code patients and capture them in health information systems they are not taken into account and end up being forgotten about

For all genetic testing, including newborn screening, it is important to emphasize that obtaining a timely and accurate diagnosis is a human right, whether there is an available medical treatment or not.

Agree. We need to overhaul the newborn screening system as it stands, and also the current criteria which dictate the policies on a national level. One way to make progress in this area could be to demonstrate the cost of a lack of efficient diagnosis, recognising that the introduction of a wider screening programme, despite the high costs, would outweigh the lifelong consequences of delays and diagnosis and all those subsequent problems that occur from the diagnostic odyssey. I think it is a matter of ethics of advocacy and of technology.

Vicki: There were never any recommendations from the EU rare disease expert groups on the topic of NBS. The closest we got was a Tender which explored the status quo and considered how heavily countries were still heavily influenced by the Wilson and Jungner criteria. That Tender produced an expert Opinion report and the EUCERD considered the outputs and came up with a list of possible topics for collaborative action, as illustrated on the KBS. There are things on that document which, 6 years later, have never been pushed forwards on any European level.

Some ERNs will be more interested in this topic than others. For instance, MetabERN is an obvious example because of the predominance of the inborn errors of metabolism in screening programs. An important next step here will be to clarify the figures countries provided, as currently presented in the KBS for this subgroup. By the end of the Autumn we should have clear up-to-date figures for all countries in Europe. Nonetheless, even with the figures we *do* have, it is clear that Europe has huge variety in NBS. This is potentially a topic where a project like this could come up with some concrete guidance or recommendations, partnering with the relevant groups.

The emergence of technology, patient empowerment and new treatments coming in gene therapy means there's a new momentum around the topic of NBS. So I think it would be time to update the thinking around it, within the ethics and the follow up with a paediatrician and so it's a broad conversation

Annex 6: Policy Consultation with the Panel of Experts on Topic 6 (Integrated, Social and Holistic Care for People with Rare Diseases)

a) What are the biggest barriers preventing people with rare diseases and their carers from receiving holistic care?

Comment/Response
Lack of knowledge about rare diseases and needs prevents people with rare diseases and their carers from receiving holistic care.
In fact, lack of knowledge can result in greater harm - There are many examples of people given the wrong advice or the wrong treatment because doctors do not have the right experience. This is bad for the patients, but also bad for society from an economic perspective, as these people may suffer long-term and be unable to work etc. Many people do not return to work because they are not given the right pathway to do this. They have been met with low expectations, and led to believe their working days are over.
Lack of knowledge amongst patients, caregivers, GPs and even the so called experts - ERNs provide some of the information - but the knowledge about ERNs is not disseminated.
Communication between health and social care is also an issue - this seems to be the case everywhere *In particular, there is no communication between the Ministry of Health and Ministry of Social Affairs or Education. There are gaps between services, no coordination and no common legislation to integrate the care services* Agree - ministries for health and social services are separate in most countries so they have different approaches. This is also reflected at the local level where social services are provided
Another barrier is that the point of view is not the same from the medical sector to the social sector. The medical sector focuses on the diagnosis, the disease. The social sector focuses on dealing with the individual situation, regardless of the diagnosis. They both speak a different language, and this is the biggest barrier. The patient however has to navigate both sides, so there needs to be a common language. The Orphanet disability project tried to provide a solution to this, but it was not enough. This dialogue and this mutual understanding should be promoted in other ways. The individual has a social situation, but because of the rare disease, the situation can be anticipated. The diagnosis should be brought to the disability people, and the personal situation should

be shared with the medical sector too.
The barriers are present everywhere with location-specific characteristics. But it is the same problem for chronic conditions in general. Health systems needs to connect to social systems in order to get a real welfare state in rare disease patients as well as chronic disease patients. Problems: different language and no data connection and no professional connection. Health and social systems usually are planned from different government departments.
Centre of competences/Expertise are very good and they do provide some social services but they mainly focus on the mission of patients. We know that they are not able to have in-home social services. We have to struggle to have this coordination between clinical care and the social care, provided at a local level. We have to reinforce the need of this dialogue between the two levels.
In Germany there is a very strict separation of the hospital and ambulant system. So many patients lose support when getting out of the hospital as case management is rarely available in the ambulant system
The problem is one of access. It can take 6-12 months just to get that first appointment. The first problem is not dissemination of information, but having the structures in place to allow people to access the system. It takes between 9-12 months to get a genetics appointment in Paris. It also takes months to get an appointment in the social system. This includes finding a school place for children with special needs. Having the diagnosis is actually not always important. The needs are the same, with or without a diagnosis
Most of the non-pharmacological therapies are not reimbursed: this is an economic burden for patients and families and seems to be the case all over Europe (according to an ERN ReCONNET study) this means that the NHSs should allocate more resources for this. An EU Directive could be useful.
The situation is as represented in the EURORDIS position paper. Rare diseases have mainly focused on orphan drugs, which has prevented a strong focus traditionally on the paramedical and social and holistic issues. Another barrier is the fact that ministries for health and social services are separate in most countries so they have different approaches. This is also reflected at the local level where social services are provided.
Many people with a rare disease 'age out' of the social support system they have, due to a lack of a life-long perspective. People with rare diseases are growing up and even getting old and the national systems are geared towards a situation where people are injured, they need treatment and are then cured. Social support, mobility aids, a handicapped parking card, all have to be applied for every 5 years. Patients have to start at the beginning every time they need a new wheelchair. There needs to be a life-long perspective that acknowledges that people born with a rare disease will most likely have it for life, and should not have to complete paperwork every 5 years. *Unfortunately, politicians make decisions according to the budget they have and too often, they do not care about long term decisions (saving money on healthcare usually). Publications and studies with the proof of concept could be very helpful.*
Many of the respondents to the EURORDIS 2017 survey mentioned that they were living in poverty. Carers are not able to work, or they are not able to work full time. The person with the diagnosis receives a very low income. It is important for people to be able to take care of themselves economically. Financial issue is crucial, especially

in low-income countries. Because of this, there is a lack of services and at the same time, financial support for carers are extremely low, if they exist at all.
In Switzerland, one of the barriers is the lack of knowledge on where the social structures are and what they provide. In the framework of the national plan, an analysis is ongoing mandate by the Swiss Federal Office to better understand what are the non-medical needs of patients, and to know where the structures are outside the hospitals. There is an urgent need to connect healthcare structures and professionals to social care and to coordinate them.
From the perspective of the Asia-Pacific region, there is a lack of expertise, knowledge and Centres of Excellence. There is also a lack of available services and resources. Most of the countries are economically deprived. **It is not always commensurate that because you do not have the resources you cannot get access to care.** It is possible that countries with low GDP or wealth have very effective, pro-rare disease policies. On the other hand, wealthy countries may not have policies or support in place. Singapore is an example of this. There can also be gaps between policy and practice. Lack of accountability is also a problem.
There is a lack of awareness about rare diseases amongst the general population in many parts of the world, and also a cultural stigma associated with rare disease.
Integrated care is difficult because it requires the implication of different disciplines and the acceptance of different budgets that belong to different Ministries in different countries. There is no consistency throughout Europe: for instance, if some countries physiotherapy / nutrition / psychological support belong to social care in other countries it is included in health care. That means different ministries, different budgets, different levels of reimbursement. How can we provide evidence of the efficacy of the overall integrated strategy as compared to the efficacy of each of its components which have different levels of efficacy one by one versus all together? In parallel how do we get each element of care reimbursed (at times by different ministries' budgets) as part of an overall integrated therapy? Should the reimbursement negotiations should target the overall integrated approach? How do we ensure proper delivery? What could be the role of the ERN? There are also different levels of prioritisation and awareness on integrated care for children and ageing population (net loss to society).
The issue of Measuring the functionality of people living with rare diseases is not only the IC but also the different procedure to score different social benefits. In some countries work breaks, job time reduction, early retirement, labour impairment and other job benefits, nursing care, disability and dependence, Psychopedagogical (special needs) assessments are individual and no coordinated processes. That brings about my different assessments, what is time consuming and exhausting, above all for children and sick persons. As a consequence inequity is present all time. It could be solved through a joint integrated processes and by a unique clinical history available to Health and social Care practitioners, sharing all clinical data and scores in different tests and scales.
The early years Schooling is, as well as transition to university or after primary school studies a gap in terms of RD policies. There is not enough health neither social assistance at this stages. School medical assistance and support is not enough for the most of the countries to achieve real inclusion. When education or schooling is not

mandatory, there is not resources. No way to receive holistic care with no taking into consideration the place where children and younghood spend half of the time of their lives.

b) What concrete good practices promote more integrated, holistic care for people living with rare diseases?

Comment/Response
We often talk about case managers who are able to help guide people through the health system. They also help people in the social care sphere. Centres of Excellence should have a close collaboration with social actors in the area. The majority probably do not do this. Having tangible case manager roles well defined would be helpful
Powerful patient organizations who started providing concepts for lifelong follow up, support and care (Started 35 years ago in Germany) - support groups for the everyday management (e.g. Kindernetzwerk) - today more in the disabled community
Patient organisations are a resource for holistic care because there are PLWRD exchange their experiences
Position paper for holistic care from EURORDIS, CEGRD Recommendation for social policies and services, Recommendations for Centres of Expertise and ERNs, Resource Centres for Rare Diseases;
Intellectual disability is one of the most common problems in Europe. This field is poorly studied in medical schools. With the exception of the Netherlands, there is no specificity about caring for patients with intellectual disability. It might be helpful to promote work like this that is already done in the Netherlands.
In Asia-Pacific region, integration of rare diseases with chronic conditions and social support for social support services, rather than asking for specific services for rare diseases is important. Regional collaborations and maximisation of services and resources is also important.
The Integral Rare Diseases Plan in Murcia was built from the regional ministry of health with the regional ministries of social issues and education. The plan is developing for the next 4 years and has an inter-ministerial commission, including patient representatives. One of the main goals is holistic care through the health-social-education connection, taking as an example the previous mental health pathway development with local commission in every health area in the region and the implantation of case management people (nurses). TICs development can also help in connecting data from social, education and health systems. Digital transformation is important. I hope this way of working may be a good practice in the future.
Use good practices and examples to create inspiration and show that things can work. There are good best practices and we know the results but we need to show that impact in a more structured way. They try to do this with Innovcare. There are a lot of challenges but at least if services and the people implementing good practices tried to systematically have some kind of evaluation, even if it's not the most refined, it's adding value

in terms of showing impact. Innovcare has an advisory group with people from different countries involved in national authorities and service. Either policy-making or more connected to service provision. There were some examples coming in such as inter-ministries working groups. There have been examples of shared budgets. Case management has raised some concerns about creating new jobs and potentially having the burden of hiring more staff. There are examples of good practices where existing staff undertake the rule of case management, either by having an enhanced involvement for example, a nurse who evolves into being case manager. Or by having some of their time dedicated to that and keeping some of their time dedicated to their main activity. The neuro resource centre in Romania has worked on getting that as a job into the national code of occupation, so that people can qualify themselves as a case manager. Coordination protocols or guiding tools help patients navigate the system, such as those developed by patient organisations in Denmark.
ERNs could play a role in ensuring best integration of care
In Madrid Spain there is an assessment centre for disability, dependence and other Social Benefits for Children is calledCRECOVI. Above this centre in the same building is located FEDER (Spanish Nacional Alliance) which is very useful for parents because they face all the assessment together at the same time and besides they receive support and advice from our helpline multidisciplinary team (built by a Social Worker, Psychologist, lawyer, and teacher for special needs) if they want to. CRECOVI and FEDER staff are here. Social Care and Health Care data are connected.
The main best practices are based on voluntary basis and come from school good purpose. Nevertheless collaboration among HCPs, HP, schools and PO experience have been very successful. Including nursery attention in different forms too.

c) How do we build momentum in advancing this topic? At national and at European/International level?

Comment/Response
We should integrate holistic/ integrated care in the NPRDs, promote case management and position paper for holistic care at national level, promote cooperation of RareResourceNet with ERNs and the development of more Resource Centres at national level;
We should build on the EURORDIS position paper on holistic care. This is the result of much work over the last seven years, with many different stakeholders. We need to find ways to implement the recommendations in this document
Mechanisms to ensure implementation of integrated care are essential. We can have a lot of knowledge, but with so many rare diseases and with so many individuals with many specific situations, knowledge is never going to be available to fully solve the problem. There has to be a way to make that dialogue, to make that coordination possible. It is important for people to understand processes, where to find the knowledge and how to work together. There need to be incentives to encourage coordinated care and to make the sectors

work together. It may not work without incentives.
NHSs should set aside more resources to reimburse the costs of non-pharmacological therapies. An EU Directive could be useful. ERNs could also contribute to patient therapeutic education
We need to perhaps consider some of the bigger issues around holistic care, particularly within the cross-border context. Need to try to address the transferability of holistic care rights for people who need to leave their home country, even for a short period. How can people retain the equipment, services, aids they have fought hard for when they move region/country? *There is no guarantee you will receive the same level of care if you move. Not even in your own country. A lot of care is locally based and funded*
We should start a deeper dialogue with disability forums, if we want to have rare disease represented in the mainstream of social services. We need to find commonalities because they are strong communities. We need to be seen as more than just orphan drug development. *Agree*
We need a way to support patients and carers living in poverty because of their situation. It is important for people to be able to take care of themselves economically
Promotion of research studies and holistic care analysing economic and social impact will be important *Agree - we need more research about holistic care to show politicians and policymakers* IRDiRC are working on research on barriers preventing patient engagement in rare disease research. It should be launched by the end of this year. Also, there is an EJP workshop in Poland in September on how social and human sciences research can improve healthcare implementation and everyday life of people living with a rare disease. This is in preparation for the 2021 joint translational research call.
People forget that national plans are supposed to structure RD activities in social systems, not just health systems. An obvious solution would be to have the body generating the national plan or strategy, and the body that is implementing it, involve people from both Ministries of Health and Ministries of Social Affair/Welfare etc. The State of the Art of Rare Diseases in Europe (SotAR) collects data on some aspects of social support and integrated care, and as soon as the updated data on this section is ready we will include it to the k.b. Summary. But it's clear from the early data that very few MS had that functioning inter-ministerial working group recommended in the past. *Having one single ministry (health and social) does not really mean that the situation is better for RD patients. There is a need for an inter-ministerial working group to enhance holistic care.* In Portugal, back in 2015, the National Integrated Strategy for Rare Diseases was jointly published by 4 ministries: Health, Social Solidarity, Education and Science. However, there has not been a budget allocation for this initiative yet. An inter-ministerial workgroup does exist, but as Vlasta pointed out, there is a huge gap between theory and putting it into practice.
It would be valuable if the HCPs who are part of the ERNs had connections to social service providers, in some, way, and try to fulfil the other EUCERD criteria for a true Centre of Expertise. That would start to have a positive

impact on the broader health spheres.
Concerning ERNs, we should work much more to get this topic onto the Network agendas, and have these issues accepted as a need, as currently they are focused on health.
Make better use of good work done in different parts of Europe. One recommendation could be that we need to promote a specialty for patients with intellectual disability in Europe. *ERNs can also play a role in raising awareness and creating information for mapping resources. Patients with intellectual disabilities will have the same abilities and disabilities regardless of which country they live in.* The leaders of the ERNs may not be aware of the European Network of Resource Centres. We need to disseminate this sort of information too
ERNs/experts should include holistic care in the best practice guidelines they produce: patients can print and use these as a support.
Need a new job function in centres of expertise/competence: case managers helping patients navigate systems. Need to on a proper career path (curriculum, continuous training, position, salary). This comes with the need to have proper inter-ministerial organisation in place. *Agree with both*
We need a knowledge database on the European level for the care and needs of patients with rare diseases on one side, and we need practical access to support on the local level for everyday life. This knowledge must be shared with local professionals including GPs so that patients have access. We have a huge deficit amongst the patients about the knowledge is available in the ERNs. Case management in Germany is part of the hospital so they only provide care and support they know. They rarely connect patients with the ERNs or national support groups.
We need a fair balance between the patients of powerful NPOs and smaller patient groups - using networks for broader possibilities for all patients.
We should work on how to scale down the position paper exchanging good practices among countries through NA and identifying common points in the way Social and Health Care are managed. The SPP is very complete but sometimes could be perceived as abstract and general to make concrete suggestions and exchanging initiatives from other countries would be inspiring and a kind of pushing for decision makers

Annex 7: Policy Consultation with the Panel of Experts on Topic 7 (Rare Disease Patient Partnerships)

a) What does true 'patient partnership' mean? How best can patients be engaged and empowered to address rare disease issues?

Comment/Responses
Need to be wary of handing over everything to patients, having patients running everything and leading everything; instead, we need to focus on co-creation, on the partnership angle
There should be a clear distinction on what a *patient* is and what a *patient organization* is. The PO is the one who helps streamlining policies and decisions to patients and brings back the patient voice to decision makers. In this context it would mean that patient organization is involved in every partnership - clinical trials, national/international awareness campaign, anything - they have the information and they act as matchmaker in every direction (among patients, doctors, industry, government, other organization
Modifying the title of the sub-group: this was an attempt to reflect a more modern and accurate role for patient involvement in the process. A lot of time they are driving the process and that's why I felt using the work partnership was a bit more accurate and there's a large movement that goes well beyond Rare Diseases and perhaps patient advocacy for some of the marginalized populations like rare diseases had something to do with it
We need to be empowered on different levels - as a patient organisation and as patient ourselves. We have tools now to make things better, but I think it needs money and time It is important to know how to detach oneself from one's own "rare disease" cause and from the defence of one's own association. What we notice inside our ERN (MetabERN) is that patient organisations still have difficulties sometimes to maintain a systemic vision It is necessary to go beyond the usual 'old demons' to build these respectful collaborations. But do not be too utopian, however, and remain pragmatic, because ultimately we are talking about the life of the disease and the vulnerable people we want to help.
There are groups of patients who are not able to represent themselves. They need parents or other types of representatives. There have been hard working parents for years now fighting for their children and now these children are growing up and needing different types of care and the parents are getting older and we don't see the same engagement for the next generation because they are so busy or don't have the capacity. Who will fight for them in the future?
From my perspective in Asia I think effective or true patient partnership scares me a little bit because this sort of imposes a huge responsibility on the partner, which in this case, in my case would be me. And I think it's important to keep in mind and to keep this In our perspective as we move along that this person who's so called representative may not be a true representative. I often hear that Asia is represented by this one person and I'm shocked for such a huge continent

Patient partnership means that the work of patients is equally recognized as valuable and the services provided by patients are accredited and integrated in the continuum of care for patients.

And the other question that's on my mind is how do countries or how do we evaluate how successfully patient advocates are recognised but sometimes they talk about patient *empowerment* quite a lot but in conferences I just see patients used for *testimonies* rather than a patient partner.

What we're talking about here is representation about the testimonies We've all sat in a meeting room, painfully hearing some personal testimonies that we're not sure of the value of after the meeting is done. And there's nothing wrong with personal testimonies If you tell it in a way that has relevance for the group that you are representing and if you actually make that connection in the same talk. You are supposed to tell a story that is relevant for your group.

One of the things I see as most relevant for the discussion for the future business sustainability of the patient engagement is how we manage the different aspects, for example of competing interest and conflict of interest with the need of the time of patients and to sustain the whole ecosystem

What does true partnership mean in basic & translational research (prior to drug development)?
In research, true partnership means integrating perspectives, needs and priorities from different relevant stakeholders (including patients and patient representatives but the range and type of other stakeholders might differ depending on the nature of the research) into one project with shared goals & objectives. See below just an indication of the different steps in which this true partnership can take place.
Step 1: Design of the research project - The partnership should start as early as possible to be meaningful and true, i.e. discussion on ideas for projects should also include the different stakeholders including patients. It means that patients sit around the table with researchers, clinicians, bioinformaticians, statisticians etc. and have a say and that their voice is heard and ideas discussed and included into the design of the project.
Step 2: Research proposal – Taking roles and responsibilities: It is the responsibility of the lead of the research project to provide scope for different type of activities to take place for which different type of stakeholders can take responsibilities. However, it is also the responsibility of the stakeholders, i.e. here patient representatives to suggest ways of involving patients within the activities of the project to provide an added value (e.g. roles in advisory, steering, scientific committees, organizing focus groups, coordinating task force, designing and carrying out surveys, communication, dissemination, input into best practices, guidelines etc.)
Patient representatives should be involved in writing of the proposal and in carrying out parts of the research project
Step 3: Monitoring and reporting: Patient representatives/patient organisations should be involved in monitoring of the activities especially but not exclusively related to patient engagement/involvement to ensure that the true partnership is actually taking place throughout the life of the project.
Step 4: Communication and dissemination: Patient representatives and organisations are not a "communication agency"! Too often, researchers will ask from patients to be involved solely within the communication/dissemination work package. Indeed, it is part of our mission, to liaise, to network, to communicate and raise awareness of the RD research projects but the role of patient rep should not be limited to this as the more meaningful and true the partnership with researchers is, the more added value and impactful the research will be. Communication needs to be a two-way process: researchers involve patients in their conferences, publications, seminars (to educate and inform other researchers about the added value that patient engagement/involvement can have in research) and patient organisations will also involve patients in their family days, conferences, newsletters etc.

How best can patients be engaged and empowered in research?
We need to change the way we do and approach research in general. It is changing but very slowly and not everywhere. It is only by providing successful and concrete examples of "true partnerships" that we will truly be able to integrate this approach in a systematic way at a global scale.
Patients need to be confident in speaking out among scientists and research professionals, they need to feel that they "speak the same language" so that they can be heard and their views, ideas integrated into the research. Similarly, researchers need to feel confident discussing their research ideas with patients. They also need to understand and appreciate the added value of a "true partnership".

Education is key at all levels and for all stakeholders. Patient empowerment will follow if capacity building takes place. Joint stakeholders training can be very effective.
Engagement of patients in research should take place at all levels, from designing the trial until promotion of the results as they are the ones that live with the disease and know the needs better than everybody: but they need to learn to understand the process.
Patient partnerships need to occur at community level. Engaging youth in this movement is very important. March of Dimes supported Volunteer Youth Leaders for Health in the Philippines as an example https://sites.google.com/site/vylhphilippines/home/aboutvylhphilippines is a
EPF has a capacity building programme http://www.eu-patient.eu/whatwedo/Capacity-Building-programme/
Language issues and translation are very important, but equally important is accessibility and sign language and making materials accessible for all people, including those with a learning disability, or hearing impairment or sight impairment.
We should focus also on patient partnership with Ministries' technicians while drafting policies related to RDs or in any action that will affect our lives e.g. identification and monitoring of Centres of Expertise
I agree very much with Simona's comment. Patient partnership should be 360° : Very often we niche the concept of partnership to research field. Although this is very important, and we are not there yet, still we should not forget the involvement and partnership in the policy domain. Partnership to me means we drive something together with mutual respect of each others' view, in a compliant way. Sometimes I think this is difficult - one actor in the field is not allowed to talk to patients directly. I also find this anachronistic - in the era of Doctor Google everybody goes to Google to find information and those who may have the proper information cannot talk and cannot contribute to make the patient a properly informed decision-maker deciding on his/her treatment and future.
Patient organisations or representatives should be involved in all fields, concerning health care, so: research, clinical trials, development of methods of diagnosis, therapies and treatment and care pathways, data management systems, outcome measures. Besides all that I see the necessity of inclusion of patient representatives into the policy-making bodies, to ensure their participation in fundamental decisions.
It is important to realize and show that 'true involvement' or 'true partnership' does not exist: it should always be tailor-made for the situation. We can show the importance AND feasibility of involvement - and the different modes that show that involvement can be beneficial in different ways in certain circumstances. We need to show this to funders, industry and academia and made sure that there are patient representatives to help organise patient involvement.

b) Are current efforts to encourage partnerships with rare disease patients sufficient? What are the bottlenecks? How can they be overcome?

Comment/Response
One of the main bottlenecks for patient empowerment is scalability and sustainability of the existing trainings.
It is important to talk about training for patients but also for other stakeholders, how to engage with other communities: because I have the experience that it's also often a lack of knowledge of how to engage with people outside their own scientific community. We had some projects where we connected scientists and citizens as well as patients, and it was an eye-opener for them. *"Speaking the same language" as researchers and or developers of therapies is not easy. This is a bottleneck. In my organisation I started a working group on Research and Care with volunteers/patients that have a background in research or care. They speak the same language. We do capacity building of these volunteers to send them to conferences/trainings that are organised by our European Patient Organisation or Worldwide Patient organisation.* *It would be ideal to have professional patient advocates being able to support these volunteers. This would make a nice team.* I think patient organisations should try to work together to have resources so that they can have paid employees working for them. Clustering of rare disease patient organisations using the framework of the 24 clusters of the ERNs could be a way forward
As a mother or a patient, living with rare disease is a lot of work besides every day life: so it's always difficult to foresee who is going to take over this work in 10 years or 20 years' time.
I think funding for patient organizations is very limited. Most work voluntarily. Foundations that have emerged from affected families may be able to help support patient organizations with less resources. *Agreed, there is a problem of financing for the patient organisations. I would highlight more the education of the patient, to empower them.* Funding is a major issue for patients organizations. On one hand, POs need to stay independent from pharma and on the other hand, they need to organize activities to achieve their goals. A transparent new working model that allow POs to be funded but, to maintain their credibility, is needed. *We have to address guidelines on how patient groups can interact with pharma companies and industry because they have the money and we are interdependent on each other. I follow Little People of America on Facebook and they had their big conference in San Francisco this weekend: they streamed a live debate where they discussed how they were going to interact with industry because the pharmaceutical companies wanted to fund their conferences and I would recommend everyone listen to this meeting recording, as they raise important issues about language that pharmaceutical companies use and also about the development of new drugs*

One big problem for patient organisations in Europe is the language barrier

I'm involved in a programme running at MIT, looking at financing and I lead the patient and care perspectives of that. One of the things that I think transfers, at least in my experience working in England and Europe, is that in rare diseases particularly, patients and carers still have financial challenges and they still face precarity in education and jobs. One of the issues that we've noted (via a systematic review and through primary research) is a really high need -identified by patients- to navigate the healthcare system and to access financial support. This is linked to a real need for financial literacy.

There is a major bottleneck of patients not being able to be advocates if they are still struggling with some of the basic needs to attain full wellbeing

Another challenge is the covering of expenses due to patient involvement - because for patient partnerships to be sustainable we have to make sure expenses are covered *and* that time taken to attend meeting can be compensated for. But at the same time, I think we do not want people making this their career aim, because we might then lose touch with our everyday patients. Patient involvement shouldn't have to be a full time job.

Perhaps we need some full-time paid patient representatives, as a model for young patient representatives. All the other stakeholders are paid professionals: why should only patients -who have such a huge responsibility and hold so much expertise- work for free and "stay poor"? If we cannot find a way to compensate people, it is likely that our communities will always be represented by only the wealthiest patients/carers or those with plenty of time on their hands (or else that patients like us end up working far too much, trying to do it all, which takes away our energy to fight our diseases). Surely the goal should be to have the most qualified people at these sorts of meetings, not just the richest? Having said this, if we do go down the route of paying people for this sort of work, it is important that the profile for such representatives is well-defined, and that they remain in close contact with other patients and families.

Agree - How can patients keep working full-time and still keep advocate? (AH)

This issue is difficult to solve, and is not black or white. I have a full time job and it is almost impossible to take enough days-off to attend at least the most important meetings.

It is important not to argue that patients should not be paid for their work, purely to avoid the idea of a 'professional' patient - I do not agree with the argument that nobody should be a full-time advocate or make this their career goal

Half of the time, nationally, I spend proving that I am a stakeholder - not only as a patient, but also as a patient representative. This is exhausting, especially, because my work is not paid. We, people in this bubble, know how important the role of the patient is, but people outside it do not really care or even try to avoid us, cutting us out of information. Coming from a vertically very strong patient organization, which always cares for our capacity and provides continuous trainings, I see other organizations are not so strong (love the clustering idea from Mariette above - we have so much to learn from each other) and many organizations struggle to get in the discussion and sometimes prefer to stay outside. This does not help with representation and collaboration.

EFPIA has policy principles which will guide most of the efforts of Industry – these highlight the right of patients to remuneration for non-promotional scopes of work. Many companies are working with patient advocacy groups in order to be able to select patients to participate to advisory boards. This helps to give funding to patients and enables patient organisation to keep the right level of monitoring on the participation of their representation to the various boards. From a company perspective there is the need for gathering more indirect information on the disease itself. The most recent approach is is also to involve patient experts into things that are more related to the design of trials and more technical elements. There is an issue related to the language and technicalities that need to be somehow addressed so the training that EURORDIS are doing are of the utmost importance to not only speak English but also the same technical language

Very few people in the patient organisations know how the health system works, also how to reach a higher level than the ministry of health: how do we makes our voices heard?

CAB (Community Advisory Boards) will be a solution to address some of the bottlenecks

Here (the US) we could possibly reduce issues to some simple types - at the risk of being reductive, so bear that in mind. Two that apply to this question:

- Heterogeneity in funding: many groups are largely developer-funded; some that are public-charity based also vary in revenue based on patient population size. This of course means that many rare disease organisations can lack the scale and funding to have enough humans and/or money to do things like network/conference

- Disease characteristics: diseases that are debilitating and/or impoverishing (in the US one is usually commensurate with the other) limits patient leadership but increases patient reliance and dependency; in turn this can make the patient organisation focus on basic service provision for their folks, and limit partnership-seeking or capacity.

a) We need clearly defined procedures for identification and designation of Centres of Expertise;

b) National care pathways should develop methods and good practice examples, to ensure patients accessibility to ERNs and Centres of Expertise;

c) National care pathways should become aligned with ERN referral systems;

d) Ongoing development of national and cross-border IT-Tools and procedures for a safe exchange of patients´ data;

e) Support, especially financial, by national health authorities and EU-Commission for ERNs and

Centres of Expertise;

f) We have to strengthen the dissemination of ERNs and Centres of Expertise to raise the awareness of the given opportunities

Annex 8: Policy Consultation with the Panel of Experts on Topic 8 (Access to Healthcare)

a) What are our most powerful 'tools' or 'assets' to improve access to high quality healthcare for every person afflicted with a rare disease in Europe?

Comment/Response
The Commission Communication on Rare Diseases: Europe's challenges (2008) and the Council Recommendation of 8 June 2009 on an action in the field of rare diseases (2009/C 151/02, EUROPLAN project and the organization of EUCERD and CEGRD (that offered the opportunity to bring together at the same table the most important stakeholders in the field of rare diseases), the concept of an ERN formed the focus of Article 12 of the Directive on the Application of Patients' Rights in Cross-Border Healthcare (often termed the 'Cross-Border Healthcare Directive') and The EUCERD adopted Recommendations on Rare Disease;
The expert teams in the different health Care Providers and visibility through ERN's and national Health care systems

b) What do you feel are the main achievements of European Reference Networks to-date, in terms of increasing access to high quality healthcare? What 'next steps' would yield the greatest progress?

Comment/Response
The establishment of 24 ERNs itself in the greatest achievement, along with the cooperation of these experts and patients around ERNs. Agree: the new culture of cooperation of experts and patient centeredness is important

CPMS implementation is also a key achievement: the CPMS is not used as much as it should be, but it is a very good tool to see undiagnosed patients or to discuss complex or severe cases where there is no known solution. The CPMS makes it possible for the experts to discuss these cases and to exchange views, and it opens up the opportunity to participate in best practice exchange at international level.

Ruth: it will be important in future to open us access to the CPMS to all CEs for RD, not just those who are officially members of an ERN. This would benefit the ERNs too, as sometimes only one or two experts are active in a network for a given disease/area, and alone these people cannot possible handle all of the difficult cases.

One problem with CPMS is that the consultations can be rather clumsy and inefficient. Is there a way to bypass the bureaucracy, but then add the information more carefully to the system later on?

ERNs are a tool that patients and clinicians and MS will shape in their role and function, based on what 'we' need. So if the CPMS isn't easy to use, then people won't use it. They may use the CPMS as a teaching and case management/discussion in an educational setting. It needs to be streamlined to meet people's needs.

The CPMS is not used much at present, but this kind of platform can be the difference between older and modern medicine

Agree - Facilitating access and streamlining the procedure will be key to success of the CPMS. Usage hurdles are way too high currently.

Another positive is the organisation of ePAG groups around the ERN - the integration of patient views into the ERN is also good

The mandatory collaboration among clinicians and countries to build the ERNs, with patient participation. FEDER for example is much more coordinated and aligned with HCP, in terms of advocacy, since the ERN challenge. The main health professionals and centers involved engage in ERNs on a volunteer basis, with no extra budget or resources, which is really inspiring meaningful. The awareness the ERN has raised of the value of exchanging information on diagnosis and treatment for RD.

In terms of next steps: a vital thing would be renewed commitment around CEs for RD: this is currently the main tool to push RD policies at European and National level.

A major positive has been in fact the attention of the Commission on providing an infrastructure for networking and reducing silos.

The biggest innovation is that experts can discuss the very, very, complex rare cases using the CPMS, sharing information on a cross-border basis in a safe and secure way with the full consent of patients.

There is massive potential around data collection with registries and the CPMS together, ideally the two being interoperable. We are on the verge of being able to collect massive amounts of data across all the ERNs, which is important given the small number of patients. We have the potential to build large datasets in a very short space of time, which holds enormous potential for the future.

Being able to gather real-time clinical evidence about patient outcomes resulting from the ERN care could become a powerful political tool, particularly for patient organisations who have traditionally been very effective in their ability to push Member States to become active in the field of rare diseases. They can be even more effective if we have evidence to prove the ERNs are adding value. The ERNs are currently looking at clinical outcome measures and they might define what those indicators are. The EC is launching a call for proposals for an organisation or consortium to set up the assessment, monitoring, information and quality improvement system across all of the Networks. This is how the information about the activities of the ERNs will be captured, which will be important in the 5-yearly evaluations.

This sort of specialised approach can also save national governments money, if patients are receiving a diagnosis more quickly, or not receiving unnecessary treatments. Looking into the economic arguments of the added value of ERNs will be important in the future.

We can all agree that the CPMS, networking and involvement of guidelines and best practices have been benefits of the ERNs. But do patients really receive these benefits directly? Do patients get access to the CPMS, or are they relying on the willingness of exerts to discuss their problem or their disease? Patients and professionals rely equally on each other. For the CPMS to work well, we should focus on making it accessible for patients. Your doctor may not agree that you need a second opinion, but you are relying on them to refer you to the CPMS panel and this most likely will not happen.

V: It is true that the 'middle part' of the CPMS process happens 'without' the patient in a sense. Patients are not present during virtual real-time reviews, for instance (to the best of my knowledge anyway). The patient is (hopefully) informed appropriate about a referral to the CMPS and reads the information sheet, then provides their infirmed consent for the case review. After this, they are not really engaged again until the point when a report is returned to their referring practitioner and (hopefully) explained to them in depth. Would there be a benefit to all patients being part of these review processes (perhaps, perhaps not – I am playing devil's advocate!)

Rebecca: Indeed, there is probably no 'one size fits all': some patients would like to be more involved, others probably not. Either way, we probably need to empower patients so they know about the CPMS, so they can at least ask for this possibility. We should keep the option open for patients to participate in the CPMS without making it mandatory. If rare disease patients are expected to be the experts in their disease, they should have access to the same information. That will also put a focus on how physicians and patients talk together about medical problems. The medical situation is what it is, whether the patient hears about it or no

Could one argue that doing so might open up the risk of more and more 'inappropriate' or not sufficiently complex cases being referred to the CPMS, purely as a result of patient pressure? When in reality, some of those cases could be well addressed by a CE approach alone?

RT: Perhaps : but the fear of the CPMS being overwhelmed by requests from patients should not overshadow the opportunity for more patients to get treatment. This could be a problem but we need to cross that bridge when it comes up.

Sometimes clinicians have to discuss cases openly with each other and it might not be the safest atmosphere for the patient.

Regarding the discussion of patient cases, we have to consider the CPMS like a normal hospital discussion. There are moments when the patient is needed and moments where the physicians need to discuss among

themselves. If during the extended use of the CPMS, specific roles are identified for patients, this could be very interesting to explore *Agree*
RB: Maybe opening CPMS for ePAGs would be a good idea: because we do a lot of counselling and may see the need of patients for a second opinion. Gabor: In Hungary, is very difficult for patients to access ERN services. The main reason is that the experts who are members of the ERN have no time to complete the necessary tasks. It would be nice if there was a controlled way, perhaps through the national alliances, to get access to the CPMS. Hopefully, if we have more members of the ERNs, these problems will be resolved, or be not as serious.
How do we reach out to 'normal' patients, who do not know about ERNs? The ERN system is very complex and the goal should be to make the whole system more visible and easier to understand for the people who need them.
There is also a language problem around ERNs, as not everyone will speak English in the next 10-15 years.
Funding is needed to facilitate networking and education for patient representatives. Remember that patient organisations do not have hospital funding behind them. A lot of them have to rely on charities and many of the small ones do not have the possibility of doing charity work, or do not want to rely on charity. Industry would be a potential source to fund patient engagement activities but currently the relationship between industry and patient organisations (certainly in the ERN context) is very unclear, in terms of what is allowed and what is not allowed. If we want this to work, and for professionals and patients to be equally dependent on each other, we have to solve these issues and define what kind of relationship is allowed with industry.
ERNs need more support from hospital providers/managers.
The EU needs to commit more effort to communicating ERN value and benefits. There is an important awareness-raising role to be done. *Agree: it is necessary to communicate the existence of ERNs more widely, for instance in areas such as southern Italy where they are not very well known (Dalia)*
To improve things, the recommendations made in the recent report by the European Court of Auditors should be considered. The funding of ERNs is also an important topic to ensure sustainability.
To improve things: ERNs should be better integrated within the national healthcare systems. There should be a fee for their services, so they can progress. *Essential to have a discussion on a European political level about integrating the ERNs into national health systems*
The CPMS is a great tool but it does not reach all of the doctors, and is not working in an appropriate way. They do not have time to meet at the same time, so it is used very little compared to what it should be. Agree. "Doodling" several experts in joint meetings is one of the most retarding elements of CPMS. The option of experts providing advice not by live conferences but by way of chats should be further developed.

It is clear that we need compensation for expert time spent on CPMS consultations and reviews; however, if there are only a few experts available in each ERN for each disease/area, all of whom have already worked a full day, then compensation for time spent on the CPMS will probably not be enough. There needs to be a larger pool of experts, where possible, to participate to CMPS activities. However, at the same time there also needs to be clear care pathways from the national healthcare systems into the CPMS. If the CPMS is used in an unregulated way, and inappropriate or straightforward cases are referred through it, you lose focus and waste expertise. The national centres which are part of each ERN should function as a 'gatekeeper' for the CPMS and the cases being discussed.
There is a major need to educate future experts in rare diseases, and this has already been one of the major achievements of the ERNs. We should consider going one-step further and think about structured curricula for the education and training of rare disease experts, and the ERNs have a particular role to play here.
The sustainability of the CPMS and the ERNs depends on the implementation of a system of compensation. But how best to address this? An important priority in terms of next steps should be addressing the disparity of access to high-end health care between Eastern European citizens and Western and Northern European citizens. Should the systems in the less wealthy countries pay for the experts in the wealthier countries, or should it be the other way around? This is an ethical and moral discussion
How can we concretely improve access to optimal healthcare *and* the access to drugs and clinical trials for new pharmaceutical compounds? The implementation of comprehensive patient registries for all rare diseases is a must. This must be accomplished in the next ten years.
There are huge cultural differences in how countries approached the development of the ERNs. Different countries have different approaches, different ways of recognising the expertise and even the numbers of patients reported by some HCPs are not based on any real data.
The main achievement of the ERN's is the visibility and Local and National recognition of expertise and formation and discussions on multidisciplinary teams and patient involvement. The access is already arranged in many places but improvements by the expected information on patient numbers, guidelines and support tools will increase the knowledge. Surgical expertise can be set in a sustainable process by the recognition of responsibility of HCP's in a longer horizon as it often is before people retire..
ERNs formalise the cooperation collaboration, which clinicians were doing informally before through personal networks and relationships.

c) What practical actions –at any level: local, regional, national, European and/or global) would yield the most meaningful results across this topic as a whole? Who should do what, and how?

Comment/Response
We need to ensure comprehensive care and follow-up from paediatric to adulthood.
We need a renewed and more strategic focus on the national mapping of expertise, formalised by comprehensive designation of Centres of Expertise for RD. Countries should not just assume that the few centres designated as ERN HCPs 9or even Affiliated Partners, or varying kinds) represent the sum total of their

expertise, or are 'enough'. ERN member centres and 'affiliated' centres should fit within wider national networks of additional CEs, designated in accordance with the agreed European concept of what a CE for RD should be and should do (the EUCERD criteria remain a good starting place). The disease-relevant criteria agreed by each ERN could be a meaningful way to reignite this national work. In very small countries, the approach will of course be different, but too many larger countries do not have a clear 'inventory' of this sort of information. If they had this, and united it with the sort of online maps already created by some of the ERNs (e.g. see ENDO-ERN), we would have a much clearer picture in Europe of the sorts of RD expertise we have, and where. *Because of the different health care systems in Finland, unfortunately there is nobody who could set the standard for how this should work. The Ministry can make suggestions but cannot enforce anything. So if nobody is willing to be an expert centre, or if the experts currently designated and approved are not the best ones, there is nothing the Ministry can do because healthcare is based on local decision-making.*
The transfer of best practices from ERNs into the national health care system is an important step forward. Organization of patient pathways and national networks for CoE that are established for the same clusters of rare diseases, communication and coordination of care, raising awareness for holistic care at national level. Patient registries are instrumental and case management to bridge the gaps between health, social and educational services for PLWRD. POs should be involved at all stages to determine the networking, sharing, cooperation and political action and support.
ERN are pushing an IT platform to exchange information among HCP and CoE at National Level. Spain as a decentralized Health System requires collaboration and data exchange to share information among countries so we can guarantee the expertise reaches, not only the patient located in the Hospital Region, but also any patient in any point of the country. EPAG initiative is also encouraging a real participation of Patient in CoE governance and monitoring (not yet, but works as a useful tool to motivate it)
It is important to bridge the gap between the more general standards of care/consensus documents that are developed within ERNs on the one side, and the more detailed and formal requirements (for e.g. of HTA bodies) for implementation at the national level.
There is a need for many countries and small centres to have better access to clinical trials and new drugs. We should plan to implement regulation, which would make it necessary and unavoidable for pharma to offer new products to patients in all European countries at the same time. Registries themselves are not a guarantee that patients will be offered clinical trials and new drugs. Registries are necessary, but do not solve the problem completely.
How do we ensure that ERNs can collaborate with other CEs for rare disease which are not formally part of their Networks? We always appreciated that there would be more centres across Europe with some level of rare disease expertise than could ever directly be members of the ERNs (in view of the sheer number of condition and the breadth of focus of the Thematic Groups). Previously, many people had envisaged a hub and spoke model, in which a small number of centres form the gateway and link to robust, (ideally comprehensive) organised and transparent national networks of national CEs for rare diseases. By and large this is not happening yet, as such organised national networks are scarce. A*gree: It is very important to create/strengthen national networks complementing the ERNs*. The hub and spoke model sounds like the only way to go, as you cannot have an ERN with 300 centres. You would need to look for common denominators between these expert centres and one such denominator is their contacts with the national alliances of those rare diseases they are working with. They all have that in common

so maybe they could be part of the hub. Attending national alliance meetings can be very interesting for professionals.
There must be clearer and more accessible routes to access a 'referral' through the CPMS. If a patient's doctor does not speak English and is not connected to the CPMs or an ERN, how can patients reach the ERN? If the different national contexts and systems won't find a systematic way to create a pathway for patients to access in an easy and timely way reference centres or ERNs, at a pace which assures equity among different member states, I assume patient advocates and respective organisations will have to push the governing structures (at national and European level) to come up with an equitable response to this need. The investment in patients' information and health literacy will, again, play its role, increasing an active participation.
It is important to retain balance - the rise of more virtual care through the ERNs (and the CPMS) should not create even more barriers for patients to see a specialist in their own country, where one exists.
Hospitals must strengthen support for the participation of their clinicians and other professionals in ERNs. The danger is that as hospital services and clinical teams are placed under increasing workloads, any 'voluntary' activities like collaborating in an ERN will be negatively affected. It is vital to strengthen that support from MS, hospitals, and fellow-clinicians.
There should be more emphasis on ERN HCPs performing their required roles. If people are not going to do the work, they should consider leaving the ERNs. This is an important issue, which has not yet been raised....
Often the criteria for ERN HCPs omits details of the requisite multi-disciplinary teams and the collaborations and the culture of dealing with patients with complex conditions. This might be improved by the collection of quality improvement systems, where we can get guidelines on who is participating and who wants to participate.
The future of the ERNs depends on whether they demonstrably deliver a structure that is better than informal networks. If not, people will slide back to informal networks. We need to focus on making the networks more accessible, including by countries that are not formally ERN members. We have to focus on making them more inclusive of other disciplines, make them more multi-disciplinary, in order for them to be attractive in future.
Policies for data protection with reference to use of the CPMS need to be urgently analysed/ addressed. This is currently a barrier for health authorities participating in the CPMS.
To increase the chances of ERNs growing stronger in future, they need to have more (legal) clout. If they had a say in price negotiations on expensive orphan drugs, or if they could exert real influence on what therapies should be provided to patients, they will be taken (even more) seriously by the European health care field.
In discussions around sustaining ERNs, it is necessary to separate the cost of the European level funding of networking and tools, from the local funding of people working in oh the different Member States.
EC should award calls based on strong plans for networking, to reduce silos