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List of abbreviations

BoMS	Board of Member States
EC	European Commission
ERDERA	European Rare Diseases Research Alliance
EJP RD	European Joint Programme on Rare Diseases
ELSI	Ethical, Legal and Social Issues
EMA	European Medicines Agency
ERICA	European Rare Disease Research Coordination and Support Action Consortium
ERN	European Reference Network
ESFRI	European Strategy Forum on Research Infrastructures
EU	European Union
FAIR	Findable, Accessible, Interoperable and Reusable
GDPR	General Data Protection Regulation
IRDiRC	International Rare Diseases Research Consortium
JTC	Joint Transnational Call
MAA	Marketing Autorisation Application
MS	Member State
MUW	Medical University of Warsaw
NMG	National Mirror Group
OR	Orphan Regulation
PaOs	Patients Organisations
R&I	Research & Innovation
RD	Rare Diseases
RWD	Real-World Data

RWE	Real-World Evidence
SMEs	Small and Medium Enterprises
TEHDAS JA	Towards the European Health Data Space Joint Action
VUS	Variants of Uncertain Significance

1. INTRODUCTION

The workshop titled **"Alignment of national rare disease strategies with the European Joint Programme on Rare Diseases (EJP RD)"** was conducted in a hybrid format, both online and in Brussels, on July 5, 2023. This workshop was organized as a specific activity under Task 2.5, which focuses on the translation and impact of prioritization on national and EU strategies within Work Package 2, "Integrative research and innovation strategy," of the EJP RD.

The primary audience for this event included key policy and research stakeholders, as well as all Work Package (WP) Leaders of the EJP RD. To facilitate meaningful discussions on crucial rare disease-related topics, the organizers of the meeting (Task 2.5 Leaders, in collaboration with Task Partners and the EJP RD Coordination Team) selected a range of subjects. For a detailed program schedule of the meeting, see Annex 1.

The workshop aimed to engage relevant policy and research stakeholders, EJP RD's Policy Board Members, representatives from Ministries and Academia associated with EJP RD, Coordinators of European Reference Networks (ERNs), members of EURORDIS, researchers, and individuals directly involved in National Plans/Strategies for Rare Diseases in their respective countries. Annex 2 provides a list of the institutions/companies and countries that were in attendance.

In this document, we will summarize the most significant points extracted from the full presentations and discussions during the workshop. For detailed reports on the presentations, see Annex 3.

During this workshop, several sessions addressed critical issues related to Rare Diseases (RD) strategies, alignment with the EJP RD, and the specific challenges faced by EU-13 countries:

Session 1:

Alignment with EJP RD Activities: This session focused on assessing how national RD strategies and plans align with the activities of EJP RD. It involved a follow-up analysis of the alignment process over the last five years, with a particular emphasis on EU-13 countries.

Development and Role of National Mirror Groups (NMGs): The development and significance of NMGs were discussed, with examples provided, such as those from Lithuania and Estonia. NMGs play a vital role in coordinating and supporting rare disease initiatives.

Session 2:

Transition from National to European RD Strategies: This session involved presentations of national RD plans/strategies, emphasizing examples and addressing the specific needs and barriers of EU13 countries (Poland and Slovakia).

Moderated Panel. A panel discussion aimed to explore how to bridge the gap between EU 15 and EU13 countries in terms of rare disease strategies. Conclusions and recommendations on European strategy were drawn.

Session 3:

Capacity Building for RD Patients: This point highlighted the importance of education in the context of rare diseases. It discussed the need for education at all levels, from early childhood to lifelong learning, involving patients, their families, medical professionals, and the broader community.

Research Infrastructures for Diagnosis and Research Translation: This point addressed the role of research infrastructure in improving diagnosis and translating research findings into clinical practice, with a focus on the impact of genetic testing. It also explored the benefits and safety considerations of using artificial intelligence in rare disease diagnosis.

Session 4:

Future of Clinical Research and Orphan Product Development: This session delved into the challenges and opportunities facing-EU 13 countries in the realm of clinical research and the development of orphan medicinal products. It included discussions on the safety and therapeutic efficacy of biological medicinal products, particularly in the context of Epidermolysis Bullosa.

Panel Discussion on Clinical Trials: A panel discussion explored whether multi-center (multinational) clinical trials could provide equal access to

reimbursement therapy and whether compassionate use should be considered as an alternative.

The workshop aimed to address critical issues such as alignment of strategies, capacity building, education, research infrastructure, and clinical research development, especially in the context of EU-13 countries, ultimately working towards improved outcomes for rare disease patients. It concluded with remarks and conclusions drawn from the discussions held during the various sessions.

The Morning Session

09.05 – 10:30

2. Session 1: Rare Diseases (RD) strategies/plans – Alignment with EJP RD activities and National Mirror Groups

09:05 – 9.25

Follow-up analysis of national state of play and alignment process with EJP RD along the last 5 years including the specific focus on EU13 countries

Laura Lee Cellai, Marta De Santis, Eva Bermejo, Domenica Taruscio, Manuel Posada, Claudio Carta (ISS, ISCIII)

National plans for rare diseases are strategic frameworks developed by governments to address the specific needs of individuals affected by rare diseases within a country. These plans aim to provide a comprehensive and coordinated approach to improve the prevention, diagnosis, treatment, and support for individuals with rare diseases and their families.

National plans play a crucial role in ensuring that rare diseases receive adequate attention and resources at the national level. They serve as a roadmap for policymakers, healthcare providers, and other stakeholders, guiding their efforts to address the unique challenges faced by rare disease patients. These plans promote collaboration, raise awareness, and drive policy changes to improve the lives of individuals with rare diseases.

Research of the national state of play and alignment process with the EJP RD project was one of the peculiar and unique tasks of WP2 of the EJP RD, which consists of

collecting information on the relevant and complementary actions performed at the national level by means of a survey.

The survey results were displayed in this presentation, gathering and updating information about the state of the art and progress made by member countries of the project in the last 5 years.

The survey examined the alignment assessment of national plans and strategies (NP/NS) for RD/other national RD initiatives with the actions of EJP RD in all (4) pillar activities with specific focus on EU-13 countries in respect to their specific needs, obstacles and advancements.

This deliverable will present a summary of the results of this presentation. For more information regarding the analysis of the national state of play and alignment process with EJP RD alongst the 5 years, please consult the public deliverable D2.24 "Fourth Analysis of national state of play and alignment process with EJP RD".

Based on the results obtained through the analysis, improvements and priority actions can be noted in 4 pillars:

Improvements (2020/21-2023):

- **Promotion of National Calls for Research Projects:**
  - Increased by 32% (from 26% to 58%).
  - Total support from NP/NS for RD in 11 out of 19 countries.

- **Promotion of Transnational Calls for Research Projects:**
  - Increased by 21% (from 31% to 52%).
  - Total support from NP/NS for RD in 10 out of 19 countries.

- **Support to FAIR Data:**
  - Increased by 26% (from 11% to 37%).
  - Total support from NP/NS for RD in 7 out of 19 countries.

- **Promotion of Rapid Translation of Research Results in Clinical Studies and Healthcare:**
  - Increased by 21% (from 21% to 42%).
  - Total support from NP/NS for RD in 8 out of 19 countries.

Actions to be Prioritized by Coming Initiatives:

- **Investments to Share Knowledge:**
  - Not supported by NP/NS for RD in 64% (12 out of 19 countries).
  - Private Funding Initiatives for Research/Networking: Lacking in 68% (13 out of 19 countries).

- **FAIR Data Support:**
  - Lack of support from NP/NS in 52% (10 out of 19 countries).
  - Lack of support from other initiatives in 78% (15 out of 19 countries).

- **Adoption of Multidisciplinary Holistic Approaches, and Data Repositories and Tools (Public and Private Level):**
  - Not supported by other initiatives in 74% (14 out of 19 countries).

- **RD Training Activities:**
  - Not promoted by other activities in 68% (13 out of 19 countries).

- **Rapid Translation of Research Results in Clinical Studies and Healthcare, and Development of Innovative Methodologies Tailored for Clinical Trials:**
  - Lack support from NP/NS and/or other initiatives in 84% (16 out of 19 countries).

EU-13 Countries Specific needs, obstacles and advancements

Taking into account specific needs, obstacles and advancements 2020/21 vs. 2023 based on Replies from 7 EU-13 Countries (Bulgaria, Czech Republic, Estonia, Lithuania, Poland, Romania, Slovakia) it turned out that the main obstacles and barriers indicated by these countries are: funding and difficulties in accessing to national resources for funding of research and development of RD projects. The primary obstacle that came to light was funding, as reported by 90% of the countries surveyed. This was followed by challenges in accessing national resources for financing rare disease research and development projects, which was cited by 80% of the countries. A smaller percentage of countries mentioned a lack of opportunities for exploitation as an issue. Only 20% of the exploitation of research outcomes at the national level were seen as a concern. Notably, in this edition of the survey, no country identified language as a barrier.

Besides above the majority of countries identified bureaucratic hurdles in funding application procedures as the primary obstacles. Specifically, 80% of the countries pointed to this issue. Half of the countries highlighted concerns about the quality of support offered by national contact points, while 43% mentioned limited connections to potential partners and a lack of information about funding opportunities. Only one country indicated that programme topics and goals were irrelevant to their research agenda.

In the latest edition of the survey, a new section was included to explore the impacts of EJP RD on three areas related to national rare disease activities. The area where countries most keenly felt the influence of EJP RD was in promoting, initiating, or aiding the implementation of rare disease initiatives that had not previously been considered or carried out in their respective countries. This had the highest impact, with 64% of countries selecting this option. Additionally, training initiatives were promoted, initiated, or implemented in 48% of the countries due to EJP RD efforts, and 36% of the countries perceived an impact on the establishment or utilization of data repositories and tools for rare disease research.

KEY POINTS

1. **Survey Trends:**
- Response trend: 21 countries in 2020, 28 in 2021, and 34 in 2023.
- Indicates an upward trend, showcasing increased interest in sharing information.
2. **National Plan/Strategy (NP/NS) for RD:**
- 22 out of 25 countries have an active or expired NP/NS for RD as of 2023.
- Survey data (2020-2023) shows 26/34 countries with active, expired, or under renewal NP/NS.
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3. **Investments in RD:**
- NP/NS focuses on national and international investments in RD
- Limited commitment from public and private funding initiatives for research and networking.

4. **2020/21-2023 Main Initiatives:**
- National and transnational calls (more than 50%)

5. **Resources and Services to foster research on rare diseases:**
- Good support to data repositories and tools for research on RD and to holistic approaches
- Improvement in support for FAIR data of 26% (2020/21-2023).

6. **Actions to Prioritize:**
- FAIR data lack support of NP/NS for RD in 52% of countries.
- Multidisciplinary approaches and data repositories/tools not supported in 74% by other initiatives than the NP/NS for RD.
- The rapid translation of research results and innovative methodologies lack support of the NP/NS for RD and of other initiatives in 84% of countries.

7. **Training Activities:**
- NP/NS promotes training in 84% of the countries.
- Other training, mentoring, and coaching activities less well-supported.

8. **Improvements (2020/21-2023):**
- Promotion of rapid translation of research results by the NP/NS for RD increased by 21% of the countries.

EU-13 Countries: Specific Needs, Obstacles, and Advancements

- **Obstacles in 2023:**
- Funding (90%),
- Difficulties in accessing national resources (80%).
- Bureaucratic hurdles in funding application procedures (86%).

- **Concerns:**
- Lack of options for exploitation of research outcomes at the national level concern for 20% of countries.

- **Additional Hurdles:**
- Almost 50% highlighted concerns about the quality of support by national contact points.
- 43% mentioned limited connections to partners and lack of funding information.
-

- **EJP RD Impact:**
- EJP RD influenced the initiation of new rare disease initiatives in 64% of countries.
- Training initiatives impacted 48% of countries.
- 36% perceived an impact on data repositories and tools for rare disease research.

09:25 – 09.40

Development and Role of the National Mirror Groups (NMGs)

Clément Moreau (INSERM, EJP RD Coordination team)

National Mirror Groups (NMGs), also known as national rare disease alliances or networks, are collaborative platforms that aim to unite relevant stakeholders within a country to address the challenges associated with rare diseases comprehensively. These groups typically comprise patient advocacy organizations, healthcare professionals, researchers, policymakers, industry representatives, and other key stakeholders.

The primary purpose of national mirror groups is to facilitate communication, coordination, and collaboration among stakeholders to improve the overall management of rare diseases at a national level. By pooling together expertise, resources, and experiences, these groups work towards enhancing early diagnosis, access to appropriate treatments and interventions, and support services for individuals with rare diseases.

The aim of this presentation was to describe the definition and purpose of national mirror groups, discuss their functions, and highlight effective ways to establish and operate these groups., divided into three main points.

1. In the first part of the presentation, the focus was on the structure of composition (with a considerable amount of autonomy) and purpose.

2. In the second part, the progress of establishing NMG among members of this project was shown during the last five years with different levels of development.

3. The last part was devoted to the future of NMG within the ERDERA Partnership.

PART 1

There are 35 countries participating in the EJP RD and the connection with the national stakeholders of these 35 countries is very essential to ensure that rare diseases research

is efficiently supported at national level. Creating Rare Diseases National Mirror Groups makes possible to create a connection as described above.

Purpose: gathering expertise and knowledge from the Rare Diseases Community of a specific country.

Key points of Composition:

- Adequate gender balance
- Wide geographical representation in each country
- A diverse representation of stakeholders (researchers, universities, clinicians, IT/data communities, ministries, funding agencies, executive/policy makers, industry/private sector, ELSI, patient organizations.

Structure:

Every country has autonomy in composition due to national circumstances, but it is highly recommended to involved stakeholders as described below:

- EJP RD Governing Board representative;
- EJP RD Policy Board representative(s);
- Relevant national partners of the EJP RD;
- Relevant national authorities (i.e. representatives of the ministry of Health, ministry of Research, etc.);
- Representatives of the National plan/strategy for rare diseases;

- European Reference Networks members;
- Research institution involved in RD research (participating to the EJP RD or not);
- Representatives of patient organisations;
- Representative of Orphanet local teams.

The objectives of a Rare Diseases' National Mirror Group are on one hand to identify national needs to be discussed and addressed, where possible, through EJP RD activities. On the other hand, promote national alignment with a European research strategy on rare diseases. These groups also have a vital role to play in revitalising the national strategic plans for research and development. Furthermore, the rest of the countries share learnings and best practices from each other. In addition, each country shares its learning and best practices with the others.

PART 2

Creating NMG started in 2019 in two countries: France and the Netherlands. Then Portugal in 2021, and the UK established itself on its own in 2022. Based on these examples, it was decided to plan the creation of NMGs across beneficiary countries in 2022 through meetings with representatives from interested countries. In the second half of 2022, a new survey was launched to gain information about existing NMGs among EJP RD members.

In the latter half of 2022, new contacts were made with country representatives to conduct a survey aimed at assessing the existence of National Mirror Groups (NMGs) in their respective countries. The purpose was to gather information on whether NMGs were in place or not.

As of now, certain countries still do not have established NMGs. Spain is currently in the process of developing its NMG associated with EJP RD. The countries that have organized working groups dedicated to Rare Diseases but are not affiliated with EJP RD include Sweden, Finland, Estonia, Lithuania, Poland, Germany, Belgium, Czech Republic, Slovakia, Austria, Italy, Slovenia, and Turkey.

Countries without any NMGs are Switzerland and Ireland, while Greece, Latvia, and Hungary have ambiguous situations due to a lack of information.

Notably, there has been no contact established on this matter in the following countries: Armenia, Romania, Serbia, Macedonia, Bosnia and Herzegovina, and Croatia.

PART 3

Future of NMGs: continuing interactions with representatives from the relevant countries, as well as maintaining in touch with current ones. When the EJP RD is finished, these efforts will be sustained for a considerable amount of time, which should result in the launch of a new ERDERA Partnership in September 2024.

To establish a Rare Diseases (RD) ecosystem it should be built on the achievements of previous programs and the approach includes:

- Advancing comprehensive research into patients' needs.
- Spearheading a Digital Transformation that seamlessly links healthcare, patient data, and research while ensuring individual control over personal data, especially Personally Identifiable Information (PII).
- Facilitating strong alignment of RD research strategies across various countries and regions.
- Organizing objective-driven Public-Private Collaborations aimed at interventions across the entire research and development (R&D) value chain.
- Accelerating the journey from knowledge to tangible impact on patients, thus maximizing the Union's innovative potential in research and development for Rare Diseases.

The goal is to expedite the translation of knowledge into patient impact by fostering strategic public-private collaborations along the R&D value chain, ultimately optimizing the European Union's innovation potential in the field of Rare Diseases.

National Mirror Groups in the context of the Rare Diseases Partnership (ERDERA)
Vision - NMGs as the voice of their national community. In order to make this vision a reality, the following actions are necessary:

- Contributing to the support of alignment and integration of national capacities into the ERDERA Partnership (through regular communications and meetings),
- Encouraging the development and the promotion of National Rare Diseases plans/strategies,
- Feeding national needs and realities into ERDERA meetings and activities (surveys on the national status quo, on NMGs activities, three-year plan development).
- Sharing of lessons learned and good practices and capacity building (annual workshop, National Alignment Board)
- Disseminating to NMG board members ERDERA activities and dissemination to national stakeholders

This task constitutes synergies between different groups in particular countries working for the benefit of each other and the broader rare disease community.

This will be achieved through different means:

- Through Annual workshops where NMGs representatives will receive trainings on key topics
- Through a day-to-day communication between NMGs
- Through the participation to Annual international Meetings within the National Alignment Board.

This National Alignment Board (NAB) will be composed of Representatives of each National Mirror Groups and Representatives of the European Commission.

The National Alignment Board will ensure that national/EU activities, strategies and needs are considered when taking decisions at the ERDERA Partnership level and when designing the annual work plans.

This National Alignment board, as an advisory body, will have a key role in determining the overall and annual planning of the ERDERA.

Therefore, this integration of NMGs within the governance of the Partnership will be strengthened and further formalized through the National Alignment Board.

HIGHLIGHTED NEEDS AND CHALLENGES FOR DISCUSSION

Identify Stakeholders: Identify and engage key stakeholders, including patient organizations, healthcare professionals, researchers, policymakers, and industry representatives. Foster partnerships and collaboration among these groups.

Establish Governance Structure: Define a governance structure that ensures representation, transparency, and accountability. This may involve creating a board or steering committee responsible for strategic decision-making.

Develop Goals and Objectives: Clearly define the goals and objectives of the national mirror group. Ensure they align with the needs of individuals with rare diseases and the broader rare disease community.

Secure Funding: Seek funding from governmental sources, philanthropic organizations, or industry partnerships to support the activities of the national mirror group. Develop a sustainable funding model to ensure long-term viability.

Foster Collaboration and Communication: Establish effective channels of communication among stakeholders, such as regular meetings, online platforms, and working groups. Encourage collaboration, information sharing, and active participation.

Engage Policymakers: Actively engage policymakers and government agencies to advocate for rare disease policies and secure their support. Participate in relevant policy consultations and provide evidence-based recommendations.

Monitor and Evaluate Progress: Continuously monitor and evaluate the progress of the national mirror group's activities.

09:25 – 09.40

Building National Mirror Groups (examples: Lithuania, Estonia)

Katrin Õunap, Biruté Tumiene, Zivile Ruzele (University of Tartu, Vilnius University, Research Council of Lithuania)

National Mirror group, Lithuania

The presentation presented the current state of National Mirror Group and general landscape in the rare disease area in Lithuania and highlighted milestones in Lithuania's participation in rare disease organisations and projects, such as: joinining to the Orphanet (2004), EJPRD (2019), IRDiRC Diagnostic Scientific Committee (2020) establishment of National Mirror Group, National Rare Disease Plan in 2012 with the organisation of conferences in the years: 2013 and 2018, Committee for NP surveillance/ Strategic Policy Committee for RD under MoH as well as existing initiatives (mentioned below) as examples of good practice for other underrepresented countries.

In terms of the most important activities, the following deserve special mention:

1. Participation in the EJP RD project;
2. Vilnius University Hospital Santaros Klinikos as an example of Competence Centers for Rare Diseases
3. The way the National Mirror Group is organised and operates/ The structure and methods of operation of the National Mirror Group

Taking into account participation and activity within the framework of the EJP RD project:

- Research Council of Lithuania is the funding agency of Joint Transnational Calls. For the period 2019-2022 the researchers and PAOs (Aniridia LT) (2021) are beneficiaries from LT in all JTC calls (RD projects);

- Vilnius University Hospital Santaros klinikosis is responsible for co-leading Pillar 3 (Capacity building and empowerment in RD research), which confirms that representatives of underrepresented countries are competent to coordinate one of the pillars and to be an inspiration to other EU-13 countries to apply for co-coordination in such complex and extensive projects as the EJP RD. In education and training section they organised training workshop: ORGANIZING & MAXIMIZING RARE DISEASE BIOLOGICAL SAMPLE DATA IN BIOBANKS on 29 – 30 October 2019 in Vilnius;

– Participation in ERNs (2017-2019): Lithuania and Slovenia – two small,

EU-13 countries with a high Full Members In ERNs:
With reference to 2 point:
The hospital bases its effectiveness on five pillars, which include the following key activities:

- **Multidisciplinary teams (**case management, psychosocial services, genetics/ other specialists according to care pathway);
- **Diagnostic >5000 RD (**genetic/ laboratory testing, pathology, radiology)
- **Complex treatments (**surgery, transplantations, special diets, enzyme replacements, genetic, biological therapies);
- **Integrated and coordinated care (**referrals, "green corridors", case management, "One-stop shop", E-health, telemedicine);
- **Patient empowerment**

in order to achieve and maintain: quality assurance, better clinical outcomes, cost-efficiency and effectiveness.

With reference to 3 point:
The Lithuanian EJPRD National Mirror Group has developed its own model for the organization and operation of the group based on regular, informal meetings aimed at and focusing on: conversations on taking part in future ERDERA and the EJPRD; conferences with the EJPRD Coordination; assistance with LT policy and EJPRD survey work; perceived difficulties and motivators for involvement; knowledge exchange and awareness-building; creating a community of diverse stakeholders.

The presentation not only provided an example of good practice that could be adapted in other EU-13 countries, but also highlighted the changes made to date for EU-13 countries over the years and projects dedicated to rare diseases in order to increase opportunities for their active participation in projects and consortia.

The following selected indicators illustrate methods to measure progress in the participation of widening countries:

1. Empowerment and capacity building:
   - Rotation of courses: 22% (8 out of 36) of all Pillar 3 courses have been or will be provided in widening countries;
   - Fellowships for participants coming from widening countries/ Fellowships for participants from various countries;

- adaptation of trainings to the local needs of participants/trainings that are tailored to individuals' specific needs.

Participants from widening countries comprised 12 to 50% of all course participants in WP14 trainings in 2019, 20% of ERN research mobility fellowships, and 10% of beneficiaries in ERN research training workshops.

2. Rare disease research funding:

   - Networking scheme ("cost-like" activities):

Funded applicants from widening countries comprised 21% (31 of 151) of applicants in the first five rounds.

   - Joint transnational calls (JTCs), widening principles:

If Early Stage Investigators or beneficiaries from widening countries are involved, consortia may have up to 8 partners instead of a maximum of 6;

Beneficiaries from expanding nations may join consortia at the second application stage (ii).

Since 2015, E-RARE and EJPRD have used widening concepts and contributed to the below-listed outcomes:

- From 1 in E-RARE-1 to 7 in EJPRD, the number of JTC funding organizations from expanding nations has expanded.
- In the EJPRD JTCs from 2019 to 2021, beneficiaries from widening nations made for 7 to 12% of the total.
- In 47% of EJPRD JTC consortia, at least one partner came from a wider range of nations.
- Beneficiaries from expanding nations received funds totaling 4,1% to 8,7% in JTC2019 and JTC2020.
- For beneficiaries from expanding nations, the average financial contributions per beneficiary were 30% to 41% lower.

Widening principles, however, might produce a situation where all consortium members come out ahead: the average amount of total money requested was 8% to 18% greater in projects that included participation from widening countries.

The Competence Centre of Rare Diseases at Tartu University Hospital, Estonia

A brief history and structure of the Competence Centre of Rare Diseases at Tartu University Hospital was mentioned, including the information on the date of its establishment (November 5, 2021), as well as the support and involvement of Children's Fund at Tartu University Hospital (a charity organization). A total of five permanent positions are retained, including clinical coordinators, nurses, social work coordinators and assistant medical doctors. The Centre is supervised by a council, led by Prof. Katrin Õunap, the presenter. Moreover, Tartu University has representatives in 20 European Reference Networks, including the one devoted to Rare Neurological Diseases.

The main objectives set for of the Competence Centre of Rare Diseases were covered, including in particular:

- multidisciplinary care for the patients with rare disease at Tartu University Hospital;
- creating and maintaining a website for efficient distribution of the information about rare diseases in Estonian language;
- active cooperation with Children's Fund – offering rapid treatment options for patients with rare disease
- active cooperation with Estonian Health Insurance Fund and Ministry of Social Affairs;
- establishing a common information space for ERNs in whom Tartu University Hospital is participating;
- Active cooperation with patient's organizations.

The regular activities within the Centre include: work group meetings, multidisciplinary discussion of complicated cases, quarterly council meetings and the organisation of the annual event on rare disease day at February 28th (29th on leap year). An average of 13 cases a month is being handled in the Centre.

The last part of the presentation focused on current issues and challenges, including:

- While the Competence Centre of Rare Diseases at Tartu University Hospital is recognized by Estonian authorities it is not yet supported financially;
- The Centre managed to prepare National RD strategy/plan in 2014, but it was not implemented to this day.

The Centre also expressed their wish towards ERDERA Partnership, including: establishing one united public procurement for new orphan drugs in all EU countries, as well as fostering collaboration in research across EU countries.

10.30 – 12.00

3. Session 2: From national to European RD strategies

EUROPEAN JOINT PROGRAMME RARE DISEASES

10.30 – 11.10

Presentation of the national plans/strategies (examples), with special attention to EU -13 needs and barriers (Poland)

Krystyna Chrzanowska, Anna Latos Bielańska, Tatiana Foltanova (Children's Memorial Health Institute Warsaw, Poznan University of Medica Sciences, Comenius University in Bratislava)

Rare Disease (RD) policy in Slovakia

The presentation presented the current rare diseases environment in Slovakia, highlighting the most notable entities, such as: University Hospital Comenius University in Bratislava, Pavol Jozef Šafárik University, Children's University Hospital, National Institute for cardiovascular diseases, National Cancer Institute, National Institute for Endocrinologic diseases, National Institute for Rheumatologic Diseases, National Institute for Children's Diseases, National screening centre. An overall of 60 centres of expertise were captioned, including 9 involved in the European Reference Network on Rare Neurological Diseases

Furthermore, the functioning and actions of the Working group for RD at the Slovakian Ministry of Health were described. The multi stakeholder group acts since 2011 and consists of 13-15 stakeholders, including patients, physicians, pharmacists as well as government officials. In particular, the activities held by the group consists of: implementation efforts (e.g. the implementation of the National plan for RD as well as other related action plans), legislative efforts (e.g. drafting legal acts, implementing European directives related to rare diseases) and sharing experience, raising awareness and disseminating the information on rare diseases (e.g. providing advice on RD, preparing informational materials, preparing expertise and participating in national and international professional events, trainings and forums related to the issue of rare diseases). The main outcomes and advantages of the Working group functioning were also presented, with the 'National health care programme for patients with rare diseases by 2030' and consecutive action plans for years 2022 and 2023 as the most notable examples.

The biggest challenges for the rare diseases field were mentioned in the last part of the presentation. Those revolved around the issues of:

- Information accessibility: a helpline for rare diseases patients is desired;
- Education: a broader scope of professions should be included, currently just the pharmacists are provided with the knowledge;
- Diagnosis, treatment and care: lack of accurate financial support to provide an efficient functioning of Centres of Expertise;
- Coordination: the creation of Coordination Centre for RD (science, social affairs) is desired;
- Data collection efficiency: broader cooperation with the National Centre for Health Information and Statistics is required;

- Inter-ministerial cooperation: actions aimed at establishing better cooperation mainly with the Ministry of social affairs is envisioned.

National Plan for Rare Diseases in Poland

The presentation outlines the development of the National Plan in Poland, from the first attempts to establish it to the gradual implementation of its individual provisions.

Legislation relevant to the field of rare diseases in the EU:

- Decision No 1295/1999/EC of the European Parliament and of the Council adopting the first Community Action Programme in the field of rare diseases in scope of public health activities (1999 -2003) appears definition of a rare disease as affecting less than 5 in 10.000 people in the general population.
- Regulation No 141/2000/EC of the European Parliament and of the Council on orphan medicinal products.
- Decision No 1350/2007/EC of the European Parliament and of the Council establishing a second Community Action Programme in the field of public health (2008-2013).
- Communication of the European Commission "Rare diseases - a challenge for Europe" (2008) indicating rare diseases as one of the priorities for action.
- Council Recommendation No. 2009/C 151/02 of June 8, 2009 on action in the field of rare diseases, in order that the member states of the European Union develop national plans or strategies for rare diseases (within the framework of EUROPLAN) for their own health systems in order to ensure access to quality healthcare, including diagnostics and treatment.
- Improved codification for rare diseases is cited as a priority in the Council Recommendation on an action in the field of rare diseases (2009).

National Plan for Rare Diseases

The inception of Poland's National Plan for Rare Diseases was initiated by the patients themselves. This effort was spearheaded by Mirosław Zieliński in 2011, who served as the president of the Orphan National Forum for Rare Disease Therapy. His passion and determination garnered support from numerous distinguished doctors, professors, and experts in the field. They collaborated to produce a professional document, which was presented to the Minister of Health during World Rare Diseases Day in 2012. Subsequently, in partnership with the Ministry of Health, the National Plan for Rare Diseases, known as the Road Map, was formulated and adopted at the occasion of World Rare Diseases Day in 2013.

Stanisław Maćkowiak, the current president of the Orphan National Forum for Rare Disease Therapy, has taken up the mantle from Zieliński and is carrying on his legacy. Prof. Zieliński had been actively involved in the development of successive versions of this important initiative for years.

The National Plan for Rare Diseases was adopted by Resolution No. 110 of the Council of Ministers on August 24, 2021, published in Monitor Polski on September 27, 2021, item 883.

The plan was developed in 2020-2021 by experts under the direction of Prof. Krystyna Chrzanowska, with crucial goals:
• improving the diagnosis and treatment of rare diseases in Poland according to the standards adopted in the EU
• improving access to high-quality and innovative healthcare services and expanding knowledge about rare diseases

The National Plan for Rare Diseases in Poland, originally scheduled for 2021-2023 and subsequently revised for 2022-2024, encompasses six primary focus areas:

- Establishing criteria for the formation of Centers of Expertise for Rare Diseases (OECR), vital for comprehensive, multidisciplinary patient care, diagnosis, and treatment.
- Outlining guidelines to enhance the diagnosis of rare diseases, including facilitating access to advanced diagnostic methods such as large-scale genomic technologies.
- Enhancing accessibility to medications, medical devices, and specialized nutritional products for individuals with rare diseases.
- Creating the Polish Registry of Rare Diseases, a valuable tool for tracking the epidemiology of rare diseases.
- Introducing the Rare Disease Patient Passport, an electronic medical document containing clinical information specific to rare disease patients.
- Developing the "Rare Diseases" Information Platform, providing clinical, scientific, and organizational information on rare diseases.

The 2022-2024 iteration of the plan includes the following key components:

- Access to state-of-the-art diagnostic services, including genetic tests like NGS and aCGH, offered by accredited and certified laboratories.
- Coordinated medical care, encompassing diagnostics, treatment, and more, facilitated by Centers of Expertise for Rare Diseases in collaboration with

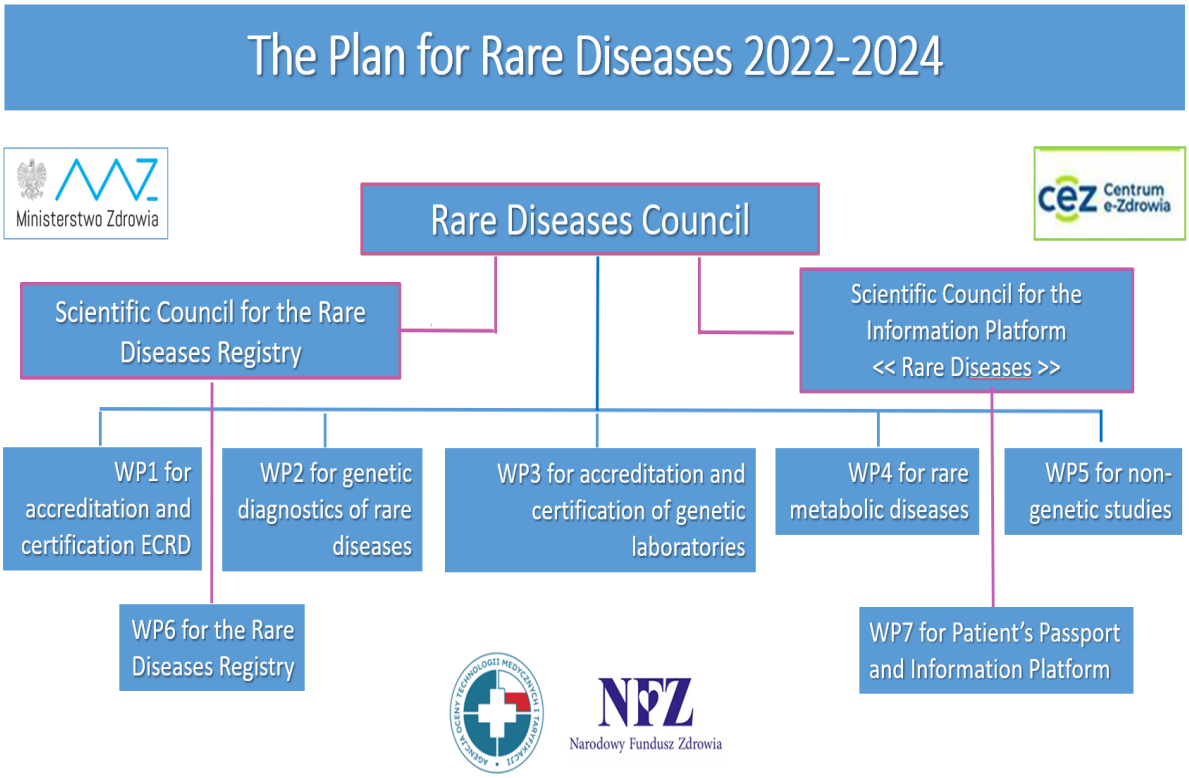
regional specialist units and primary care facilities. Ultimately, the goal is to establish a nationwide network of Expert Centers for Rare Diseases.

- Geographical mapping of rare diseases through the Rare Diseases Registry, enabling access to Centers of Expertise and other necessary care for specific patient groups. This aids in epidemiological research and healthcare planning, with involvement from the Ministry of Health (MH) and the National Health Fund (NHF).

- Implementation of an Information Platform dedicated to "Rare Diseases" and the introduction of a Patient's Passport (electronic) with open emergency access.

Structure: three advisory bodies and their chairs

Rare Diseases Council: Prof. Anna Latos-Bieleńska
Scientific Council for the Rare Diseases Registry: Prof. Krystyna Chrzanowska
Scientific Council for the Information Platform: Prof. Anna Kostera-Pruszczyk



Interim Outcomes in Implementing the Rare Diseases Plan:

- **Genetic Diagnostics:**

The Minister of Health has appointed the initial Centers of Expertise specializing in rare diseases, based on their recognized competence. These centers are also members of European Reference Networks (ERNs), and currently, there are 46 Polish centers belonging to 21 ERN networks.

The Ministry of Health plans to appoint more such centers, following the recommendations of the European Union Committee of Experts on Rare Diseases (EUCERD). The ultimate goal is to establish a comprehensive national network of Centers of Expertise for Rare Diseases (OECRs).

The Ministry of Health is receiving support in formulating legal regulations in the field of laboratory medicine. Efforts are underway to develop legal regulations concerning genetic testing, with a draft submitted in May 2023 and awaiting legislative action. Criteria for the certification of genetic laboratories have been devised, and an electronic application process for laboratory certification has been established. The Polish Society of Human Genetics will conduct the next round of certification for genetic laboratories in September 2023.

The Ministry of Health and the National Health Fund are actively working on introducing new genetic services, including genetic testing and consultation, with reimbursement mechanisms.

- **Centers of Expertise for Rare Diseases (CERD):**

The primary objective is to enhance the diagnosis of rare diseases. The focus is on improving patient access to diagnostics and multidisciplinary, well-coordinated medical care, aligning with current knowledge and technological advancements.
Large-scale molecular diagnostic services are provided by Medical Genetic Centers, while Genetic Outpatient Clinics serve as Expert Centers for Rare Diseases. These centers operate with interdisciplinary teams consisting of specialists in various fields, including clinical genetics, molecular genetics, and bioinformatics. The emphasis is on genetic diagnosis for personalized therapy.

- **Information Platform "Rare Diseases" (chorobyrzadkie.gov.pl):**

The platform contains sections for news, general information about rare diseases, services, healthcare providers, patient organizations, registers, education (including an Encyclopedia of Rare Diseases), and a portal team.

- **The Polish Registry of Rare Diseases (PRRD):**

This registry has national coverage, acting as an epidemiological database for rare diseases in Poland.
It is designed to exchange data with European registries, adhering to the FAIR principles (Findable, Accessible, Interoperable, Reusable).

Phase I involves patient data submissions to the registry by Centers of Expertise for Rare Diseases and genetic centers/outpatient clinics (including Polish ERN members and new centers designated by the Ministry of Health through a competition).
The registry employs the ORPHA codes, nomenclature, and Orphanet classification catalog via an electronic submission form. It can be utilized to identify potential candidates for clinical trials and research studies.
Planned training initiatives are part of the Orphanet OD4RD2 project and the National Plan for Rare Diseases.

Additionally, apart from the National Plan for Rare Diseases, the National Oncology Strategy, a long-term program implemented from 2020 to 2030, plays a significant role in advancing genetic diagnostics in Poland. This strategy, adopted by the Council of Ministers on February 4, 2020, introduces comprehensive changes to Polish oncology.

Summary and Conclusions regarding Poland's National Rare Disease Plan, along with Highlighted Needs and Challenges

- **Conclusions:**

Enhanced Medical Care: The Rare Disease Plan is expected to lead to a significant improvement in medical care for patients with rare diseases.

Improved Genetic Diagnosis: Access to genetic diagnosis will see improvements, including the introduction of advanced high-throughput genomic testing methods, which will contribute to better recognition and understanding of rare diseases.

Specialized Centers of Expertise: The establishment of Centers of Expertise will provide long-term, targeted medical care tailored to the unique needs of rare disease patients.

Patient Visibility: Through the use of ORPHA coding and the issuance of patient passports, individuals with rare diseases will become more visible within the healthcare system, facilitating better care and support.

Information Platform: The Rare Diseases Information Platform will serve as a comprehensive and easily accessible source of reliable information on rare diseases, benefiting both patients and healthcare professionals.

Legislative Catalyst: The Rare Diseases Plan is acting as a catalyst for numerous legislative changes in Poland, promoting a more supportive environment for rare disease management.

HIGHLIGHTED NEEDS AND CHALLENGES
Genetic Testing Regulations: There is a need for clear legal regulations governing human genetic testing, including standardizing the commercial market to ensure quality and ethics. **Certification of Genetic Laboratories:** The certification of genetic laboratories is crucial to maintain high standards of testing and ensure accuracy and reliability. **Reimbursement for Advanced Testing:** Securing reimbursement for advanced genetic testing methods like aCGH and NGS is essential to make them accessible to patients. **Qualified Personnel:** Adequate staffing for genetic diagnostics and genetic counseling is needed to meet the growing demand for these services. **Certification of Non-Genetic Laboratories:** Specialized non-genetic laboratories also require certification to ensure they meet the required standards for rare disease diagnostics. **Comprehensive Medical Care:** Access to comprehensive medical care, including innovative therapies, for patients with rare congenital heart diseases (CHDAs) should be ensured. **Education and Awareness:** Education programs for primary care physicians and specialists in the field of rare diseases are necessary to improve diagnosis and care. **Reliable Information Sources:** Access to reliable sources of information on rare diseases is essential for both patients and healthcare professionals. **Legal Improvements:** The jurisprudence related to rare diseases should be improved to ensure that patients receive the necessary legal support and protections. **Removing Barriers:** Efforts should be made to remove barriers that hinder access to education and the labor market for individuals with rare diseases. **Social Solidarity:** Building an atmosphere of social solidarity around people with rare diseases is important to ensure they receive the support and understanding they need.

In conclusion, Poland's National Rare Disease Plan is making significant strides in improving the care and support for individuals with rare diseases, but there are still important needs and challenges that must be addressed to fully realize its goals. These include legal and regulatory reforms, investment in healthcare infrastructure, and increased awareness and support within society.

11.10– 11:50

Moderated panel with policy makers on bridging the gap between EU 15 and EU 13 and the European strategy

Piotr Fiedor, Milan Macek, Georgi Iskrov, Oleg Kvlividze, Carlos Almeida Pereira (Warsaw Medical University, Charles University Prague, Medical University of Plovdiv, Agency for Clinical Research and Biomedical Innovation)

The MUW was responsible for organising the panel, raising an important issue, especially from the perspective of the EU-13 countries.

The questions were presented during the workshop, allowing the participants of the workshop, apart from the invited panelists, to respond.

Furthermore, after the workshop, questions for both panels were sent to all participants in the form of forms to be filled in, giving them the opportunity to respond to the issues raised. during the panel sessions.

The objectives and selection of questions for the panel discussions were agreed with the decision-makers indicating the need for public discussion and the choice of a common strategy allowing for the joint implementation of strategic goals in the national programs of rare diseases in all member states.

List of questions

1.What is the experience in developing and implementing a rare disease programme/plan/strategy in your country?

2. For therapies that have been approved by EMA, how do you think that the time until they can be used by the patients can be shortened?

3. How are patients involved in the implementation of RD strategies, and how to improve this involvement?

4. What should be changed in the system of European strategy of EU member states (thirteen countries and fifteen countries) with current experience so that the process of access to therapy and to grants, EU programs, education (goal- leveling skills), infrastructure can be fair and effective?

5. What are the most important conclusions and recommendations from the actions taken so far to improve diagnosis, research and access to the latest therapies for patients with rare diseases?

6. How is currently the equity on treatment access represented by the regulations and laws? and how to improve the equity at the policy level?

The 13 Member States report similar targets and challenges for rare diseases. Leveling the playing field in the areas of diagnostic, clinical and educational infrastructure is the main objective.
The creation of common clinical databases requires the development of a uniform legal regulation for Member States in order to freely and legally exchange medical data, which will allow for the unification of procedures for early genetic diagnosis.

In order to achieve above the following actions are essential:

- **Establishment of specialist centres for the diagnosis of rare diseases for the needs of population-based, large-scale studies with full access to diagnostics in cooperation with primary care physicians.**

- **Centralisation of Specialist Rare Disease Systems, which will be networked and will provide full access to registries. The database platform can be used for ML and AI research in screening for rare diseases.**

- **Patient access in clinical emergencies will be provided by an electronic passport for patient safety in life-threatening situations**.

Analysis

Genetic diagnosis is important in two groups of patients, those with rare diseases and cancer patients. It is the basis of personalized therapy, which has enormous potential. It uses high-throughput genomic testing and requires laboratories that are equipped with specialized equipment and a well-trained staff of laboratory geneticists and computer scientists. The genome data should be protected, and it is also crucial that it is centrally collected because of the rapid growth of information on a given population's genome, in this case, the Polish population, as this facilitates the interpretation of genomic results. Genetic testing must be of the highest quality, and therefore proper supervision of genetic laboratories must be necessary.
There is an urgent need to adopt a law on genetic testing, comprehensively regulating genetic diagnostics. Eighty percent of rare diseases are genetic. Genomic diagnosis in rare diseases includes prenatal testing, i.e., fetal testing, testing in living individuals in both children and adults, and genetic testing in deceased individuals, which is currently not covered by reimbursement in Poland and is also not regulated by legislation. The methods of genetic testing used in the diagnosis of rare diseases are classical cytogenetics, and finding applications through molecular genetics, but primarily are high-throughput genomic testing and simple molecular methods (PCR and modifications, Sanger sequencing, MLPA, and others).

Rare disease patients usually do not have the option of effective therapy. In any case, establishing a causal diagnosis, and identifying the molecular defect is extremely important for the individual patient and the entire family. Diagnosis ends the diagnostic odyssey typical of rare diseases, limits diagnostic hospitalization, and enables therapy with an available drug. Early detection of the disease by molecular testing means sparing the patient from many diagnostic tests, sometimes invasive and aggravating. It also saves the budget and reduces the cost of the entire diagnosis, in each case, by as much as 80%.
For instance, in Poland reliable data showing a comprehensive age cross-section of patients, including adults, stating that as many as 25 to 40 percent of patients in the waiting rooms of specialty clinics, all of them not just in expert centers, are patients with rare diseases. Unfortunately, most of these patients will never know that they have a rare disease unless we decide to effectively implement some systemic solutions. Most of these patients are the ones who, at some stage of their disease, and sometimes from the beginning, require multispecialty care. Sometimes, multiple people in the same family get sick. Therefore, is it necessary to map patients to know where the medical need is. There is a passport for a patient with a rare disease and an information platform.

Bulgaria was the second EU Member State (after France) and the first Eastern European country to officially adopt a national plan for RDs (2009–2014). It stated nine main priorities, including the creation of a national registry, the expansion of newborn screening, and improved diagnostics for RDs. Nevertheless, some of these goals were not fully achieved. Adoption of a second plan to carry on these activities was discussed but never materialised.
The current political focus in Bulgaria regarding RDs is on three priorities: designation of centres of expertise and their integration into the ERNs, expansion of newborn screening and optimisation of the current national registry for RDs.

Access to new innovative therapies is really one of the most important benchmarks of RD policy. It is a complex issue involving multiple stakeholders at different levels (EU and national). Two key issues are seen here that could help address the inequalities in access across different Member States.
The first is the ongoing work on the Proposal for a Regulation of the European Parliament and of the Council laying down Union procedures for the authorisation and supervision of medicinal products for human use and establishing rules governing the European Medicines Agency, amending Regulation (EC) No 1394/2007 and Regulation (EU) No 536/2014 and repealing Regulation (EC) No 726/2004, Regulation (EC) No 141/2000, and Regulation (EC) No 1901/2006. There is a need for stronger requirements for market authorization holders to launch medicinal products with an EU-wide authorisation in all Member States. Currently, medicinal products like orphan drugs are market authorised via a centralised procedure, but then companies prefer to focus on large markets and often ignore small Eastern European Member States. This situation is particularly troublesome and fundamentally unfair.
The second key issue is the implementation of Regulation (EU) 2021/2282 of the European Parliament and of the Council of 15 December 2021 on health technology assessment and amending Directive 2011/24/EU. Health technology assessment helps improve and accelerate access to innovative treatments at the national level. So, the centralised cooperation on health technology assessment at EU level is expected to

have positive spillover effects on all Member States and the access of RD patients to newly approved therapies.

Participation of RD patients in the process of policymaking is a must. And this is now a standard practice across all Member States. In Bulgaria, RD patients were part of all stages of the national plan, from preparation to implementation. RD patient representatives are now engaged in the process of designating local centres of expertise. There are two sitting members of the Bulgarian Ministry of Health's Commission on Rare Diseases who are RD patient representatives. So, RD patients are now equal partners in all fields of RDs.

One key issue will be the ERNs. The ERNs are really the most critical RD infrastructure now; they concentrate large amounts of expertise and knowledge, and their potential to contribute to all RD domains is enormous.
A problem that could be further addressed by RD policy measures is the unequal participation and engagement of centres of expertise from smaller Eastern European Member States. For example, Bulgaria is currently represented in only a third of the ERNs; there are no Bulgarian centres of expertise in the vast majority of the ERNs. So, Bulgarian RD stakeholders are basically excluded from what is going on in these networks.

Another problem is the unclear legal status of the local centres of expertise for RDs. Right now, these entities are kind of virtual. They do not dispose of their own personnel and resources, meaning that the centres of expertise need to "borrow" them from the existing healthcare providers. Lack of specifically allocated resources and the strain of bureaucracy put off many experts from engaging in ERNs. What could help address this deficit in legal status are explicit recommendations from the EU on the scope, status, activities and funding of these entities. Such a uniform EU-wide approach could be the best incentive to take action at the national level.

If ERNs are sustainable and effective, their added value will be transferred at the national level as well. So, RD patients could benefit from improved diagnosis, treatment and follow-up wherever they live. This is why the EU should take action in two specific directions. One is to make sure that each Member State is represented in all ERNs by at least one local centre of expertise. Second is to adopt an official EU recommendation on the scope, status, activities and funding of ERNs and local centres of expertise for RDs.

On paper, all policies, including RD policies, are based on the principles of equity and equality. The problem comes with practical implementation. We see inequalities between different EU Member States and within individual EU Member States as well. So, it is a big problem.
One way to address this issue is to allocate more resources to RD patient populations that are particularly disadvantaged. But more resources do not always automatically mean better health outcomes and smaller inequalities. There must be mechanisms and stakeholders to oversee this process, and here again lthere is the potential role and impact of the ERNs.

As a Non-EU Collaborating partner, Georgia, represented by the Georgian Foundation for Genetic and Rare Diseases, took part in the Europlan 1 (2020-2011) and Europlan 2

(2011-2015) projects, however, Georgia did not have its own National Plan/Strategy. In 2022, by order of the Minister of Health, a working group was created in order to write NP. The draft document has been submitted to the MOH in Apr. 2023 and already approved. The final version of the NP will be ready in Nov 2023.
The structure of the Georgian National Plan, according to the recommendations of EUROCERD, includes all the main goals, the achievement of which is associated with a radical optimization of the State policy on RD: methodology and management; definitions and codification; research and clinical trials; education; reference centers and ERN; orphan drugs; diagnosis and treatment issues; social support

Georgia is still a non-EU country. The principles of RD treatment financing that exists in Georgia are the following. Unfortunately, in Georgia the treatment of rare (genetic) diseases is not covered by the state or private insurance. At the same time, there is a state (federal) program on RD that finances hospital, outpatient (under 18 years of age) and medication (orphan drugs) service for patients with more than 40 rare nosologies. This program assumes that all patients with a verified diagnosis will get treatment for the rest of their lives. To date, the allocated budget for this program is approximately 11 M euros, which is growing significantly every year. Also, the treatment of rare diseases is financed from municipal budgets, as well as within the framework of the state referral treatment program (by the concrete case).
To date, this principle of financing in a country with relatively limited financial resources allocated to health care justifies itself, however, given the rapidly growing number of orphan drugs approved by the FDA or EMA, it is likely that in the near future it will be necessary to develop new (more advanced) design of RD therapy reimbursement with the active use of successful European experience. In particular, in making such decisions, it is necessary to evaluate the current HTA in case of a particular orphan medicine.

In Georgia, patients are involved to varying degrees in decision-making and strategy development in the field of RD. In the aforementioned group for creation of NP on RD, more than 20% are patients or their representatives. Patients are also present at almost all meetings of the National Coordinating Council for RD founded based on the MOH, as not only most interested, but also a full-fledged party when discussing a particular issue. It was difficult to imagine such a thing in Georgia a few years ago, and this process is progressive.
What contributed to this? The answer is: the time that took patients to acquire knowledge, international relationships and advocacy skills. That is, to improve the process of involvement in the development of strategies in the field of rare diseases, time is needed, it itself will put everything in its place. It also requires (and it's an extremely important) active support from the government of patient initiatives (in particular, any support, even up to support at the level of tax legislation and subsidized programs for the activities of patient organizations).

Taking into account equal access and standards, similar level of infrastructure, participation in EU programmes, more effective cooperation in consortia, balanced parity of countries in consortia.

Georgia not being either a representative of the EU 15 or EU 13 countries, makes it very difficult to talk about this issue. At the same time, the most effective mechanism for achieving fairness and efficiency in providing access to treatment and grants for all

EU countries is the intensification of joint research, educational, clinical or diagnostic EU programs (including with the active involvement of a big pharma and diagnostic laboratories). At the same time, a number of these programs should a priori assume a certain level of increased responsibility of the more economically developed countries to the other in the frame of EU. ERDERA is a good example of this approach. It might also be useful to have more EU 13 representatives in the ERNs.
So, the key word to achieve the above goal is the word "more", more programs, more contacts, more collaboration to create a common unified model (carcass) of RD management within EU countries.
Georgia being a member of the IRDiRC FCC, considers the recommendations developed by IRDiRC WGs in 2022 to be among the most significant, pragmatic, and success-oriented recommendations for improving diagnosis, research and access to contemporary treatment for PLWRD.
In the world of rare diseases and the often long diagnostic odyssey that patients endure, it is evident that new tools are needed to improve the overall patient experience, identify new treatments, and reduce the socio-economic burden of rare diseases.
These recommendations form the basis for continued collaborative work amongst the international rare disease community in order to reach a collective goal to "Enable all people living with a rare disease to receive an accurate diagnosis, care, and available therapy within one year of coming to medical attention".
The recommendations were created in accordance with the following goals:
Goal 1: All patients coming to medical attention with a suspected rare disease will be diagnosed within one year if their disorder is known in the medical literature; all currently undiagnosable individuals will enter a globally coordinated diagnostic and research pipeline
Goal 2: 1000 new therapies for rare diseases will be approved, the majority of which will focus on diseases without approved options
Goal 3: Methodologies will be developed to assess the impact of diagnoses and therapies on rare disease patients.

Surely, the very principle of providing equal access to therapy for PLWRD is not subject to discussion, and it should ideally be so. Another question is how to achieve this in practice, based on the constant improvement of diagnostic methods, and, accordingly, the increase in the number of patients with RD, as well as the annual increase in the list of FDA/EMA-approved orphan drugs, and, at the same time, with a limited state budget? Strange as it may seem, but in Georgian legislation/practice, dedicated to treatment issues of patients with RD, ethical and moral principles are reflected to some extent: if the government finances a particular rare disease, then all patients with a verified diagnosis receive treatment, regardless of age and for life (of course, if there are no age restrictions for therapy).
However, let's return to the issue of improving the legislation of Member States. this issue is very important, but it is not the most relevant at this stage in the formation of optimal models of management/treatment reimbursement of RD. As of today everything is simple and clear: If there will be more money for treatment, there will be more responsibility on the part of government and big pharma, there will be more access to treatment for all PLWRD. As paradoxical as it may sound, consideration of issues of ethics and morality in this situation is not of an abstract nature, but is quite acceptable in relation to big pharma and, in part, governments, although it is not clear how they should be reflected in legislative acts.

In France, the impact of the first three Rare Disease National Plans has been profound, significantly shaping and supporting the research and care landscape for rare diseases. Notably, the establishment of competence centers and reference centers has given rise to competence clusters addressing the myriad rare diseases. The inception of Rare Disease Sectors ("filières") at the national level served as a precursor to the formation of European Reference Networks (ERNs). As the fourth plan takes shape, it is anticipated to be finalized by early 2024.
Patient involvement is pivotal in implementing Rare Disease (RD) strategies, and enhancing this engagement is crucial. Patient advocacy organizations (PAOs) play a vital role as collaborative partners in various aspects. They contribute to data collection, capturing the disease's natural history, a critical element in evaluating new treatments. PAOs also pinpoint specific needs of patients to enhance their daily lives and actively support research on their particular diseases, urging the scientific community to focus on these conditions. To enhance patient involvement, fostering a "research culture" within PAOs is essential, emphasizing the significance of scientific research and elucidating the research process, both preclinical and clinical.

In the past decade, the Czech Republic has made significant strides in developing and implementing a comprehensive rare disease program. The journey began with the adoption of the first National Strategy of Rare Diseases (2010-2020) during the country's 2009 EU Council Presidency. This strategy was subsequently implemented through three successive National Action Plans. Notably, the establishment of the National Coordination Centre for Rare Diseases has played a pivotal role in fostering both domestic and international collaborations, including active participation in European Reference Networks (ERNs). Legislative initiatives, such as the Genetic Act of 2011, integration of the term "rare disease" in healthcare legislation, and participation in international agreements, have further strengthened the country's commitment to rare disease research and diagnostics.
Czechia's engagement extends to numerous European Union projects, such as RD-Connect.eu and Solve-RD.eu, and the coordination of the national hub of Orphanet. The country's involvement in the EEA/Norway grants scheme specifically addresses the healthcare needs of the Roma minority with population-specific recessive disorders.
In Lithuania, the funding agency LMT is a member of the EJP RD consortium and is set to participate as a partner and beneficiary in the ERDERA partnership. Despite this involvement, LMT does not currently have a national program exclusively focused on rare diseases, and consequently, it is not actively contributing to the formulation of a national rare disease plan or strategy that would synchronize with research funding initiatives in the field.
To enhance patient access to approved therapies, Czechia involves patient organizations in decision-making, although challenges arise with the budget impact of gene therapy orphan medicinal products. In Lithuania, establishing mechanisms for timely information dissemination and incorporating procedures in national rare disease strategies are suggested to expedite the adoption of newly approved therapies.
Regarding patient involvement in rare disease strategies, Czechia integrates patients into the decision-making process through legislative procedures. In Lithuania, there is room for improvement, with proposed measures including building a common understanding among policymakers, encouraging proactive engagement by patient

advocacy organizations, showcasing examples of good practices, and facilitating dialogue between patients, policy makers, and national institutions.
Czechia asserts an equitable healthcare system as per its legislative framework, while Lithuania explores avenues to enhance equity at the policy level.

Panel discussion between representatives of the EU-13 Member States and proposed common position and conclusions

Panel remarks and summary-Conclusion and recommendation:

1. Diagnosis and reimbursement therapy: equitable access to diagnostics and treatments based on cooperation between Member States to support inadequate infrastructure in the EU 13
2. Clinical outcome: joint research and clinical platforms between the EU-15 and the EU-13
3. Decisions at the level of the European Commission: credible cooperation and accountability of policymakers
4. Streamline the facilitation of clinical trials for rare diseases.
5. Develop robust clinical research networks to strengthen collaboration and information exchange.
6. Establish comprehensive data banks at the European level to enhance accessibility and sharing of valuable information.
7. Promote translational research, with a particular emphasis on innovative biotherapies, including gene and cell therapies.
8. Advocate for national resources dedicated to clinical trials and market utilization for ultra-rare diseases, fostering public-private partnerships under a complete public umbrella.

The following issues were also discussed during this panel:

1. **What has changed and improved in the access of under-represented countries since 2006 (JTC implemented by the ERA-Net E-Rare) and now in the EJP RD, taking into account their participation and contribution at national and European level?**

A long-term strategy has been in operation for quite some time, aiming to close the gap between underrepresented countries and countries that have gained significant importance in research and innovation, strategic alignment, and institutional positioning in recent years. This strategy has been in place since 2006, starting with the first Joint Transnational Call (JTC) initiated by the ERA-Net E-Rare and continuing up to the current phase of the European Joint Programme on Rare Diseases (EJP RD). During this period, specific measures were implemented, particularly focused on facilitating the participation of consortia that include countries located in peripheral areas of Europe those countries still striving to establish competitiveness on the global research and innovation stage. As a result, there has been a noticeable increase in the involvement of underrepresented countries in JTCs, leading to a more equitable

distribution of European funds among countries that were previously less influential in the central European research landscape, as evidenced by statistical data.

2. **What kind of discrepancies between countries' performances in what respects to R&I are still in effect?**

Despite the efforts made by EJP RD to boost the involvement of underrepresented countries particularly through measures introduced for Joint Transnational Calls (JTCs), these countries still continue to encounter distinctive challenges when it comes to their participation and contributions within the European and international context. This perspective is supported by various official reports that have highlighted these challenges. Consequently, it is believed that, despite institutional initiatives, there remains a notable absence of a systematic approach aimed at enhancing underrepresented countries engagement in EU programs. This viewpoint is supported by consecutive reports from ERA-Learn.

Even though underrepresented countries are increasingly participating as partners in consortia funded by JTCs, they typically assume subordinate roles and seldom take on coordinating roles or central responsibilities in proposal submissions.

Furthermore, when considering activities beyond JTCs within European initiatives such as EJP RD (including mobility actions, training programs, or the integration of work package tasks), underrepresented countries participation appears to be even more limited. From institutional perspective, these disparities persistently exist and represent variations in performance among countries.

3. **In the context of the preparation of the future Rare Diseases Partnership (ERDERA), what is the plan to close the gap or eliminate/redress inequalities between high- and low-performing R&I countries and increase the role of EU-13 countries using their unlocked potential in participation in the European Programs and JTC?**

In the context of the ERDERA Partnership, addressing inequalities is an urgent concern, especially given that underrepresented countries make up approximately 70% of the ERDERA partners, spanning 20 out of 29 countries. Given that the ERDERA aims to be a pioneering initiative actively working to narrow the gap between countries with high and low performance in the field of Rare Diseases, it is logical to prepare specific measures to tackle these inequalities and unleash the full potential of underrepresented countries and their value within the ERDERA.

Conclusions

The panel discussed several key issues related to the access and participation of underrepresented countries (UCs) in research and innovation (R&I) programs, particularly in the context of rare diseases:

Progress Since 2006: Efforts have been made to bridge the gap between UCs and countries that have assumed central roles in R&I processes. Measures implemented since 2006, including special conditions for consortia from peripheral European areas, have resulted in increased UC participation in Joint Transnational Calls (JTCs) and a more equitable distribution of European funds beyond central Europe.

Continuing Discrepancies: Despite these efforts, UCs still face challenges when participating in European and international R&I landscapes. Official reports also highlight these challenges. A systematic approach to enhance UC involvement in EU programs is lacking.

Subordinate Roles: UCs often assume subordinate positions in consortia funded by JTCs, rarely coordinating proposals or taking on central roles.

Limited Participation in Other Activities: UCs have limited participation in activities beyond JTCs in European initiatives like the European Joint Programme on Rare Diseases (EJP RD).

ERDERA Partnership role

Regarding the preparation of the future ERDERA Partnership, the plan aims to address these disparities and unlock the potential of UCs:

Pressing Inequalities: UCs represent a significant proportion of ERDERA partners. The ERDERA seeks to proactively address inequalities and leverage UCs' potential and added value.

Key Objectives: The plan focuses on addressing specific UC needs, fostering collaboration, and enhancing UC participation in R&I programs.

Transversal Efforts: Achieving these objectives will require coordinated efforts, including mapping capabilities and assets, capacity development, advocacy, awareness-raising, and knowledge sharing among UCs.

Undertaking advocacy and awareness efforts to UCs added value – for instance, synergies with ERN Network (JARDIN), EURORDIS, HNN3.0, NFP4EU, and NCP_WIDERA.NET | identification of UC assets, populations, and expertise of value to R&I efforts.

Creating an Inclusive Ecosystem: The goal is to create a more inclusive and impactful R&I ecosystem, unlocking UCs' potential within the ERDERA.

Emblematic Efforts: Key efforts include promoting capacity development, undertaking advocacy and awareness initiatives, supporting UC participation in ERDERA activities, and facilitating mobility actions for UCs, especially for PhD students, Postdocs, and medical doctors in training.

In summary, the panel discussed also about the progress made in addressing disparities between UCs and other countries in R&I programs, the remaining challenges, and the plan to close the gap and increase the role of UCs in the future ERDERA Partnership. The focus is on addressing specific needs, fostering collaboration, and enhancing UC participation to create a more inclusive R&I ecosystem.

The Afternoon Session

The afternoon session was dedicated to improving access and uptake of new medicines in Europe. There is a need for accelerating innovation ecosystems and new entrepreneurships, which can be fulfilled by contacting research institutions, academia, industry (SMEs) and investors. Training researchers inEU13 countries is very important for progress in diagnostic and to raise the competeness and the need to implement innovation in rare disease treatment regimens.

13.00 – 14.20

4. Session 3: Capacity building to ensure equity and optimize outcomes for RD patients

Rare Disease education for sustainable development

Rare diseases have long been one of the top public health concerns in Europe, and they are now increasingly being recognized as a global public health priority, with calls for action coming from both high- and low-income nations.

The importance of education on rare diseases from an early age to lifelong learning (all school levels, patients and their families, doctors and medical staff)

13.00 – 13.20

The importance of education on rare diseases from an early age to lifelong learning (all school levels, patients and their families, doctors and medical staff)

Birute Tumiené, Vilnius University faculty of Medecine, VUH Santaros Klinikos, Coordinating CenterFor Rare Diseases, The Head ERN board of member states, Orphanet Lithuania, National Coordinator European Joint Program on Rare Diseases, Pillar 3 Co- Leader, IRDIRC Diagnostic Scientific Committee, Roseline Favresse, Research Policy & Initiatives Director, Eurordis

The lecture has emphasized the value of lifelong learning and early education on rare diseases. The participation in shared activities can maximize the potential of the various stakeholders involved in the EJP RD and beyond, as demonstrated by international RD activities. The many elements that make up the EJP RD have been outlined for this purpose.

Capacity building is needed to ensure equity and optimize outcomes for patients with rare diseases.
Education for sustainable development is necessary, In the first presentation of the afternoon, needs and challenges were presented.

In Europe, rare diseases are defined as those affecting up to 5 people per 10,000 population, and rare cancers are those with an incidence of less than 6 people per 100,000 population per year.
Approximately 6,000 to 8,000 Rare diseases are currently known that can affect any organ or body system at any age, and in most cases, Rare diseases are multisystemic, so doctors of any specialty will consult with patients living with a rare disease (PLWRD). With a point prevalence of 3.5 to 5.9% (excluding rare infectious diseases, poisonings, and rare cancers, which together account for about 20% of all cancers), PLWRD make up a significant portion of our society], but they still face huge unmet needs.

To address gaps in the knowledge and awareness of current and future healthcare workers and equip them and the multi-stakeholder rare disease and rare cancer community, with a solid foundation of knowledge and skills to face the many challenges associated with rare diseases and rare cancers, there is a need to devise a common education and training strategy in Europe and beyond that too.

It must be developed and implemented by a number of education and training providers: universities, medical and nursing schools and their associations, professional bodies, European reference networks, patient organizations, other organizations and institutions dedicated to Parkinson's disease and other diseases rare cancers, governments and political institutions.

Together, they ensure coherence and complementarity to education and training across the rare diseases and rare cancers ecosystem.

International cooperation is essential in the field of rare diseases and rare cancers, and provides the means to harmonize educational standards in different countries and globally.

It is necessary to identify gaps and needs in many areas: for different professions and majors and from the perspective of learners based on the presented pyramid principle.

The foundation of this pyramid consists of a general knowledge base and includes broad stakeholder groups such as students and general practitioners; The top of the pyramid refers to highly specialized knowledge and knowledge generation, including experts and opinion leaders.
Because the fields of Parkinson's disease and rare cancers have many similarities but also important differences, there is an opportunity to share some best practices and solutions between the two fields and a need to identify strategies are sometimes at different levels of education and training (e.g., the urgency of diagnosis in rare cancers will be much greater and require "red flag" teaching).

.

For each stakeholder group and disease, educational outcomes need to be clearly defined and educational programs and frameworks must be developed (including training requirements, curricula, and resources, education, etc.)

Finally, national, international and professional policies and strategies must support education and training on rare diseases and rare cancers, such as the European Reference Network strategy on education. Recently developed training and priority given to rare diseases is one of the strategic directions of the Association of Faculty of Medicine in Europe.

HIGHLIGHTS FOR THE DISCUSSION
• Detect disease/establish diagnosis • Definition of clinical presentation/natural history study • Evaluate disease mechanisms and biomarkers/disease formation • Model Determining treatment goals • Identify appropriate treatments (drugs, devices, surgical interventions, diseases management) • Identify meaningful outcome measures (clinical/surrogate/ patient-centered) • Clinical trials/observational studies

- Transition science/post-market surveillance/implementation/de-implementation science
- Develop evidence-based clinical practice guidelines and resources
- Continuous improvement cycle

The objective of the EURORDIS Open Academy School on Medicines Research & Development, often known as "Summer School," is to equip patient advocates for rare diseases with the information and abilities necessary to become authorities in pharmaceutical research and development. Since 2015, the School has now welcomed researchers (8 to 10 per session). The School has educated 551 people from all around Europe and beyond since it opened in 2008. The School's primary subject areas are as follows: development of treatments for rare diseases, methodology, design, and ethics of clinical trials, regulatory routes for orphan medications, pharmacovigilance, taking action by involving patients. The course consists of pre-training webinars and online learning modules that must be completed from January through June, as well as one week of in-person training that is currently offered in June in Barcelona.

13.20 – 13.40

Prevention of social exclusion in rare diseases – forms of education for children and adolescents

- **Experiences of EU Countries in creating educational standards in rare diseases**

Anna Rypniewska, MD., Medical University of Warsaw, Poland

The presentation concerned educational resources on rare diseases developed in recent years. It was highlighted that awareness of these resources is still limited and rare disease education is still not sufficiently addressed by key stakeholders such as academic and professional organizations. The need for a fundamental rethinking of the issue of education in the field of rare diseases was highlighted and work towards a common, coherent and complementary strategy for education and training on rare diseases in Europe and beyond.

The presentation drew attention to the fact that people living with rare diseases still face huge unmet needs, in part due to the fact that care systems are not sufficiently aligned with their needs and healthcare workforce along their care pathways lacks competencies to efficiently tackle rare disease-specific challenges.

Level of rare disease knowledge and awareness among the current and future healthcare workforce is insufficient.

In recent years, many educational resources on rare diseases have been developed, however, awareness of these resources is still limited and rare disease education is still not sufficiently taken into account by some crucial stakeholders as academia and professional organizations. Therefore, there is a need to fundamentally rethink rare disease education and healthcare workforce development across the whole spectrum from students to generalists, specialists and experts, to engage and empower, People living with rare diseases their families and advocates, and to work towards a common coherent and complementary strategy on rare disease education and training in Europe and beyond. Special consideration should be also given to the role of nurse coordinators in care coordination, interprofessional training for integrated multidisciplinary care, patient and family-centered education, opportunities given by digital learning and fostering of social accountability to enforce the focus on socially-vulnerable groups such as PLWRD.
This strategy should be developed and implemented by a variety of rare disease education and training providers: universities, medical and nursing schools and their associations, professional organizations, European reference networks, patient organizations, other organizations and institutions dedicated to rare diseases and rare cancers, authorities and political bodies.

HIGHLIGHTS FOR THE DISCUSSION
Some specific aspects of rare disease education and training need improvement: • Care coordination: the roles of case managers and nurse coordinators • Multi-professional training in integrated multidisciplinary care • Patient- and family-centered rare disease education: • "Patient expert" and patient empowerment • The power of online learning and the need for digital literacy • Professionalism, social responsibility, safety and cultural responsiveness • Constraints and benefits of diagnostic and national (social and therapeutic) programs for patients. The influence of education on enhancing patient acceptance.

• **Barriers and benefits of diagnostic and national programmes (social and therapeutic) for patients. The influence of education on increasing patient acceptance.**

Anna Rypniewska, MD., Medical University of Warsaw, Poland

During the presentation, attention was paid to activities aimed at shortening the diagnostic path (the so-called diagnostic odyssey) and developing new therapies. The issues of access to care, including primary health care and new technologies and telemedicine, were also discussed.

In discussing the benefits and barriers to diagnostic programs, issues facing patients with rare diseases are also discussed.
At the international level, respecting the vision and goals of the International Rare Diseases Research Consortium (IRDIRC) is needed and helps planning and developing what is needed.

Working groups address the needs of the rare disease community. Actions should be aimed at shortening the path to diagnosis (called the diagnostic odyssey) and development new therapies, stimulating multi-stakeholder engagement and clinical trials. Also access to care, including primary care and new technologies or telemedicine, and partner strategically with patients and healthcare organizations while growing impact assessment method.

HIGHLIGHTS FOR THE DISCUSSION
• complex diagnostic maze, • diagnosis is lengthy, tedious, frustrating and costly for patients, their families and the health system, • a significant proportion of patients are not diagnosed in a timely manner, simply due to lack of awareness and coordination of health systems and pathways, • primary or local care specialists do not have sufficient knowledge and are suspicious of DR • knowledge of the health system to guide patients to the correct level and point of care

- ***Research infrastructures to foster diagnosis and research translation for RDs for diagnosis and clinical research. State and development***
  (Anna Rypniewska, MD., Medical University of Warsaw, Poland

The second part of the session focused on the role of building research infrastructure and the role of clinical trials. As published in Document 2.1 (D2.1) "Final List of Prioritization Criteria" Priority criteria should be used to structure the mapped needs and activities that contribute to achieving EJP RD research objectives. The EJP RD proposal identifies four general criteria: aspects of scientific evidence, demand from the R&D community, legal and social, financial and technical considerations, feasibility.

13:40 – 14:00

Infrastructure as a key to diagnostic effectiveness in the diagnosis of rare diseases and the impact of genetic testing on treatment implementation.

Iwona Maroszyńska, Institute of the Polish Mother's Memorial Hospital , Poland

The presentation focuses on the effective functioning of highly specialized centers related to the diagnosis and treatment of rare diseases. *The need to further develop prenatal screening and testing was emphasized, as was the need to establish centers that provide comprehensive care for rare diseases.*

The following presentation highlights actions to support and advance all rare diseases. The need to expand strategies and plans to develop diagnostics and care for patients with rare diseases was emphasized. This framework should include comprehensive patient care at a highly specialized center: testing and diagnostic capabilities, access to the most modern forms of treatment and qualified medical staff. It is very important to be able to perform newborn screening tests for diseases such as: Congenital adrenal hyperplasia, Congenital hypothyroidism, Cystic fibrosis, Biotinidase deficiency testing, Spinal muscular atrophy (SMA), Amino acid metabolism disorder, Phenylketonuria, Organic aciduria, Fatty acid oxidation disorder. The Institute of Complex Fetal to Adult Medical Care at the Polish Mother Memorial Hospital in Łódź, Poland, is considered a model for the establishment of this type of reference center. It is one of the largest centers of its kind in Europe.

Another problem is the sharing of scientific data between research centers, which is seen as a threat to weaken its position in the face of international competition.
It is recognized that for data standardization and interoperability, actions are required to create platforms (including the EJP RD virtual platform), i.e. the need for this platform has been recognized over the years before.

Training and the need to make innovations in the treatment of rare diseases are very important treatment protocols.
These challenges can be addressed by the new IRDiRC and joint working groups.
There is a need for further collaboration and integration with other infrastructures (e.g., the European Health Data Space [EHDS], the European Medical Research Consortium infrastructure [EU- AMRI] connecting medical research infrastructure [EATRIS-ERIC] - focuses on translational medicine - ECRIN -ERIC - focuses on international clinical trials -and BBMRI-ERIC – focusing on biobanking and biomolecular resources).

HIGHLIGHTS FOR THE DISCUSSION
Access to consistent quality data can support industry engagement and Development plan: - tools that contribute to the exchange and dissemination of clinical research results and technical innovations, - understanding between the rare disease community, patients, communities and regulators, - exchange of information between patients and the institution about research methods, reimbursement policy details, - develop non-profit alternative medicine development models, thereby raising awareness of cost definitions among users and the RD community. - Innovative therapeutic mechanism, discussion and development of new costs discount and payment model.

14:00 - 14:20

Safety and benefits of artificial intelligence in the diagnosis of rare diseases: between innovation in research and good medical practice

Grzegorz W. Basak, Professor and Chair, Department of Hematology, Transplantation and Internal Medicine, Medical University of Warsaw

The presentation emphasized the need to develop artificial intelligence in medicine. It was emphasized that the use of artificial intelligence could bypass some conventional limitations related to rare diseases. Namely, it can optimize traditional randomized control trials and ultimately reduce drug research and development costs.

The use of artificial intelligence (AI) in healthcare has grown in recent years.

It has also demonstrated its potential to improve diagnostic and treatment effectiveness. Certain types of AI, such as machine learning, can effectively analyze large data sets, identify patterns, and generate important insights.

Predictions can then be made to provide personalized medical diagnosis and treatment recommendations. The use of AI can avoid some of the common limitations associated with rare diseases. Specifically, it can optimize traditional randomized controlled trials and potentially reduce drug research and development costs. Recent advances have allowed researchers to train models on large data sets and then fine-tune those models on smaller data sets often related to rare diseases.

A prime example of the use of artificial intelligence in medicine is Saventic Health, a medical and technology company that relies on creating algorithms to help doctors treat rare diseases, based on association with algorithms and artificial intelligence tools.
Diagnosing rare diseases is currently very difficult. This is because doctors only see them occasionally and do not have the opportunity to gain experience in the field.
Specialized knowledge in this field is difficult to access, is often non-specific, and has irregularities in clinical trial results. Access to experts equipped with parts is very difficult. Therefore, the process of diagnosing a patient can take several months or even longer and can also occur due to diagnosis or lack of diagnosis.

Saventic Health's algorithms shorten the time needed to make an accurate diagnosis, reduce diagnosis costs as well as patient treatment costs, thereby improving treatment effectiveness. Solutions based on artificial intelligence tools are monitored in relation to personal data from healthcare.

The developed and validated algorithms are ready for use in backend entities using the dedicated SARAH facility via local deployment or remote instructions using a dedicated API in JSON data.
Integration with the computer system of the units provides the results of the algorithm, sent directly to the device located at the external interface (in the member device).
In fact, Saventic Health is launching and deploying algorithms to support specific diseases across three locations: leukemia and rare hematological diseases, metabolic diseases, maximal deficiencies. The company's goal is to expand the algorithm's expansion into rare diseases, including skin and other diseases, neurological diseases and more.

The capacity to conduct research and introduce new technological products in rare diseases therapy must be strengthened by improving the ability to share relevant research on rare diseases through the creation of common resources and validated analytical tools.

HIGHLIGHTS FOR THE DISCUSSION
• *active patient participation in population and epidemiological studies to improve the ability to analyze results,*

- *enhance availability of relevant data through better communication with legal and social stakeholders;*

- *enhance the ability to translate basic research into advanced therapies through connections with commercial and nonprofit funders.*

The common exchange of knowledge and results in the search for effective models of sustainable development is of great importance because it is the only opportunity to overcome barriers of misinformation and difficulties in collecting and sharing data between partner countries.
The objectives have been identified in the document titled "Proposed Activities: European action plan Rare Diseases" and focuses on ways to promote European leadership in R&I, to reduce premature mortality from DR as well as the economic, social and psychological burden of DR and its delay.

5. Session 4: The future of clinical research and orphan product development – challenges and opportunities for EU13 countries

The lack of capacity to translate basic research into advanced therapies through linkages with commercial and nonprofit funders makes this cross-border research collaboration even more difficult, beyond in addition to providing health care services. The themes and barriers (and therefore, needs) of infrastructure, law, trust and transparency in the TEHDAS JA report are as follows. National laws/regulations are heterogeneous regarding research and health data beyond GDPR, with varying exemptions (Legal).

The lack of standardized data sharing agreements with the private sector has hindered public-private collaboration. We know that there is a need to accelerate new innovation and startup ecosystems, which can be achieved by reaching out to research institutes, universities, industry (SMEs) and investors.
The training of researchers is as important to improve diagnostics and increase competitiveness as is the need to implement innovation in treatment regimens for rare diseases.

Additionally, targeted training for researchers will improve their skills and competitiveness, facilitating diverse career paths and mobility between industries.
Overall, European R&I policies aim to strengthen innovation cohesion and increase competitiveness of the entire EU, which was confirmed in discussions based on presentations by experts.

14.20 – 14.40

Research and development of new medicinal products in the EU 13 Member States: Biological medicinal products-safety and therapeutics efficacy on the example of treatment of children and adults with Epidermolysis Bullosa

Cezary Kowalewski, Professor, Medical University of Warsaw, Poland

The Orphan Regulations (OR) are still being developed, but the feedback and impact report from the public consultation process (published in November 2021) revealed significant obstacles most notably:

The presentation was about building the capacity to perform or contribute to the positive impact of Research on the example of testing a biological innovative dressing in the treatment of EB. An important issue was to present the challenges and obstacles that scientists encounter when

The introduction of new drugs involves underdevelopment of unmet needs, inequities in the availability and affordability of treatments, and inadequate adoption full range of scientific and technological developments, as discussed in the previous presentation.

Epidermolysis bullosa (EB) is a group of rare genetic skin diseases, also known as dermatoses, characterized by severe chronic blistering that leads to painful and life-threatening complications.
Despite previous and ongoing advances in this field, there is still no effective etiological treatment for EB. Treatment is limited to the relief of symptoms, which, depending on the severity of the disease, may be related to the skin (vesicles, wounds that do not heal at the slightest mechanical irritation, contractions) and abnormalities of internal organs (esophagus, pylorus or duodenum); renal failure and hematopoietic abnormalities).
The past decade has been marked by a series of important discoveries that have paved the way for new treatments, including gene therapy, bone marrow transplantation, cell therapy (allogeneic fibroblasts, mesenchymal stem cells [MSC] and the use of induced pluripotent stem cells in tissues).
Experts at the Engineering Clinic are working to develop skin-like structures that can facilitate the healing process to promote skin regeneration of currently incurable wounds.
However, this is really a challenge due to the complex structure and many functions of the skin. During the presentation, EB was described and its potential treatments were presented. Although a cure for EB remains elusive, recent data from animal models

and the first human clinical trial have increased the expectations of patients, clinicians, and researchers.

Therefore, it is possible to modify the course of the disease and improve quality of life. In addition, the results of EB treatment could significantly improve the treatment of other genetic diseases. This is why the prioritization and allocation of grants must be clear, equitable and transparent to all EU 13 stakeholders.

As noted, the BiOOPA dressing is readily available, safe, and relatively inexpensive, making it a promising treatment for EB-related wounds.
Preliminary results from the BIOOPA study indicate that bandaging is safe and effective in improving study subjects' quality of life.
Currently BIOOPA is being evaluated in a phase I/II clinical study in its second year of observation. The clinical trial results clearly show that this innovative dressing is a promising strategy and tool for clinicians in the search for new treatment opportunities for this rare disease.

Despite the tremendous progress made in treating Alzheimer's disease, current treatments are clearly not a cure for this debilitating disease and the risks associated with some procedures must be weighed against their potential benefits.
Effective treatment of this currently incurable group of RD requires advanced and innovative strategies with improved safety profiles, such as those currently being discussed at these EJP RD workshops.

HIGHLIGHTS FOR THE DISCUSSION
To benefit from the positive impact of research, new technologies and advanced therapies in an RD project, it is possible to: *• strengthen capacity to conduct research and introduce new technological products in the treatment of rare diseases, by enhancing the ability to share relevant research on rare diseases by creating resources Common principles and validated analytical tools,* *• active Patient participation in demographic and epidemiological studies to increase the ability to analyze results,* *• enhance capacity to provide relevant data through better communication with legal and social actors;*

14:40 – 15:15

Panel discussion: Do multi-center (multinational) clinical trials solve the problem of equal access to reimbursement therapy or should be used a compassionate use?

The MUW was responsible for organising the panel, raising an important issue, especially from the perspective of the EU-13 countries.

The questions were presented during the workshop, allowing the participants of the workshop, apart from the invited panelists, to respond.

Furthermore, after the workshop, questions for both panels were sent to all participants in the form of forms to be filled in, giving them the opportunity to respond to the issues raised. during the panel sessions.

The objectives and selection of questions for the panel discussions were agreed with the decision-makers indicating the need for public discussion and the choice of a common strategy allowing for the joint implementation of strategic goals in the national programs of rare diseases in all member states.

List of questions

1. How are the international clinical trials in rare diseases (collaborations) affected by the legal context and heterogeneity on legal regulations between EU member states (sharing sensitive medical and scientific data for clinical purposes for patients)? Which are the solutions?

2. What do we expect from clinical trials, including research on new medicinal products to improve the quality of life of Patients? Whether we need a common medical database to improve the treatment of Patients?

3. On this basis, should the unification of costs and analysis of the criteria for inclusion in pre-registration be implemented and what standards should be implemented in clinical trials (including international ones) for patients with rare diseases?

4. By whom it should be conducted/carried out and reimbursed clinical trials and compassionate use therapies? (governments, European institutions/programs, pharmaceutical companies)

5. Should recommendations for effective diagnosis and treatment with AI be included as one of the most issue in national programmes in EU member state?

Comments and recommendations of the Georgian Foundation for Genetic and Rare Diseases

On the example of Georgia - Participating in clinical trials, no members of the Foundation experienced any problems in terms of sharing confidential information. However, it is possible that this is due to the fact that Georgia is not a Member State. Surely, there is no doubt that clinical trials are a powerful tool to ensure that patients have access to treatment. Based on this, even if there are any legal problems, their active implementation is fully justified from the standpoint of reducing the burden caused by rare diseases.

Proposed solution until uniform legal regulations for the EU countries are elaborated, temporarily, outside the legal field, allow the exchange of medical and scientific data of patients included in clinical trials.

Moreover such standards (unified criteria and maybe also cost) should definitely be developed. This will greatly facilitate and make more efficient the conduct of clinical trials. However, the very process of their development, and it is possible that it is quite long, should not serve as an obstacle to the inclusion of patients in multinational clinical trials.

From non-European country point of view, the practice of partial reimbursement by government of the cost related with clinical trial incurred by Pharma is in line with the principles of justice and is a powerful impetus for actualization and, accordingly, in the long term, successfully solving the problem related with RD, which occurs in most, if not all EU countries. At the same time, since government funding for the RD treatment, in particular, in the Member States is progressively growing, and commercial risks for pharma are progressively decreasing, it will be appropriate to gradually and reasonably reduce the amount of government reimbursement for the cost of clinical trials.

Regarding the recent news about the achievements related to artificial intelligence, and from the other side the frankly ambiguous public reaction to this, it is questionable that in the near future issues related to the diagnosis and treatment using AI will become a priority topic for Member States, even in the frame of elaboration of relevant EU regulations.

Discussion on the second panel

1. The discussion focused on the issues of equal opportunities in the Member States and the unification of the educational process at the level of kindergartens, schools and, above all, social awareness in families. It is important to introduce a subject discussing rare diseases and diagnostic and therapeutic possibilities in medical studies for future doctors into the education process.

2. The panel discussed and indicated the most important directions of the strategy and unification of legal procedures with the necessary legislation and implementation for all member states. The EJP RD programme was rated very highly, and it was found that the programme assumptions for individual Member States caused a strong resonance in the international and political environment, and above all in the area of public health, and increased expenditure on diagnostics, genetic testing and treatment of rare diseases.
3. Another topic concerned the development of a common protocol for clinical trials and endpoints, as commercial and non-commercial clinical trials do not currently require specific legal solutions and regulations in multicenter trials and there may be a free (information is coded and confidential) exchange of medical data between countries in international trials. This problem should be urgently resolved in the European Commission.
4. Policymakers in the panel, based on the presented lecture on the early diagnosis of rare and oncological diseases and the selection of the most effective therapy, pointed to the important importance of artificial intelligence in medicine, and above all in the genetic diagnosis of undiagnosed rare diseases and the selection of adequate treatment in personalized medicine in the area of oncology, which should be covered by joint funding and regulations.

Conclusion and recommendation of the panel :

Education: The strategic role of the development of the rare diseases program in the European Union member states requires continuation in the areas indicated by the EJP RD panelists and concerns primarily a greater emphasis and political involvement in the educational processes of the society, from the education of policy makers, children, adults and medical personnel, including the development of an education program for students in the field of public health (physiotherapists, teachers in kindergartens and schools
Legislation: It is necessary to amend the legal provisions to allow for the free exchange of research results between academic and clinical centres and the creation of common databases for the analysis of clinical data in undiagnosed cases and the need for genetic development in order to make a diagnosis and the most effective therapy based on artificial intelligence. An integrated data system is expected, and at the moment there are no legal provisions allowing for the exchange,
Clinical trials: It was assessed that clinical trials in rare diseases require a unified protocol for non-commercial and commercial clinical trials on therapeutic efficacy in the form of defining the endpoints of the trial in a protocol with the participation of the regulator i.e. the European Medicines Agency. Multicentre research in rare diseases will allow for the creation of a unified R+R+I infrastructure and an ecosystem of clinical sites with European funding approved by the European Clinical Research Agency,
Social exclusion: Proposal to submit another programme to the European Commission for financial support for social education and access to diagnostics and therapy, including reimbursement of medicines in the integrated system of meeting the criteria of access to treatment. Increased funding is needed for programmes for the development of new orphan medicines. Unequal access to diagnostics and therapies is the most important problem to be solved today in the face of the planned European development strategy in the field of rare diseases as well as precision medicine.

Regulations allowing for the creation of an integrated system and legal access to national patient databases, tissue banks and medical data is an elementary strategic problem in early diagnosis of rare diseases, including genetic testing.

The key-points summarizing the most important conclusion of the panels:

Common tasks in the strategy for rare diseases in the Member States require equal opportunities in EU 13 and unification of the implementation of tasks concerning the most important areas of joint development of subsequent programmes concerning:

1. common research and education policy,
2. research infrastructure-genetic diagnostics,
3. running common medical databases with the use of artificial intelligence (AI) for the needs of multicenter clinical trials

15.15 – 15.30

Remarks and Conclusions

•Integrate and optimize the care pathways and social and daily needs of patients with MR to achieve comprehensive care (including access to treatment, care and support appropriate psychosocial support in a patient-centered manner).

• Digitalization of healthcare, access to information, telemedicine, enabling and improving access to remote consultation for patients with rare diseases worldwide.

• Access to diagnosis and medication.

• Advances in personalized medicine.

• Provide effective and equitable health care to patients with rare diseases.

• Enhance the capacity of physicians, patients and families and share knowledge across borders.

• Quality care, with new care models, focusing on sustainable development.

• Accelerate the orphan drug licensing process, facilitating the regulatory process for potential therapies and drug repurposing, including access after regulatory approval.

• Facilitate global strategic collaboration through infrastructure and diagnostics tools/instruments/platforms/data sharing (accessible diagnostics ecosystem and coordination).

• Identify potential regulatory barriers to shopping cart testing.
Build capacity to combine innovation, research and entrepreneurship (training of trainers, linkages to national programmes, coaching).

• Facilitate the adoption and implementation of RWE in healthcare decision making. Marketing

• Request Authorization (MAA) based on RWE.
Identify synergies with regional, national, European and international IRs and strategies for optimal use.

• Access to orphan drugs by small or underdeveloped countries.

• Increase the attractiveness of the pharmaceutical industry thanks to clear criteria (financial and non-financial).

• Identify barriers to accessing standard care products.

• Facilitate and improve data sharing in health research (EC spaces/ecosystems, e.g. European Health Data Space (TEHDAS), Health Research and Innovation Cloud Europe (HRIC), OpenScience)

• Capacity building on the drug development pathway for therapy developers.

• Health economics research through dedicated calls and funding, as well as support for HTA, standards and evidence

• Identify scientific, legal and regulatory issues related to emerging therapies and technologies and support research and development procedures.

• Develop legal and ethical contracts to collect and share health and genetic data, including appropriate consent (ELSI framework) for data sharing and innovative technologies existing as artificial intelligence.

6. Conclusions of the workshop

Common tasks in the strategy for rare diseases in the Member States require equal opportunities in 13 countries and unification of the implementation of tasks concerning the most important areas of joint development of subsequent programmes concerning:

Main Obstacles in Rare Disease Research:

- Funding is the primary obstacle, reported by 90% of surveyed countries.
- Challenges in accessing national resources for RD projects are cited by 80% of countries.
- Limited opportunities for exploitation were mentioned by a smaller percentage.

Additional Insights:

- Only 20% expressed concerns about soft research outcomes at the national level.
- Language was not identified as a barrier in this edition of the survey.

Barriers Indicated in Survey:

- Bureaucratic hurdles in funding application procedures were identified by 86% of countries.
- Concerns about the quality of support from national contact points were highlighted by half of the countries.
- Limited connections to potential partners and a lack of information about funding opportunities were mentioned by 43% of the countries.

Impacts of EJP RD:

- EJP RD had a significant impact on promoting, initiating, or aiding rare disease initiatives in 64% of countries.
- Training initiatives were promoted, initiated, or implemented in 48% of countries.
- 36% perceived an impact on the establishment or utilization of data repositories and tools for rare disease research.

National Mirror Groups:

- National stakeholders must include patient organizations, healthcare professionals, researchers, policymakers, and industry representatives.
- A transparent and accountable governance structure should be established with goals aligned with the needs of individuals, that should engage policymakers, advocates for rare diseases policies, and provide evidence-based recommendations.
- Seek funding from governmental sources, philanthropic organizations, or industry partnerships.
- Foster collaboration, communication, and active participation among stakeholders.
- Continuously monitor and evaluate the progress of national mirror group activities.

Competence Centre of Rare Diseases:

- Covered multidisciplinary care, information distribution, cooperation with relevant entities, and establishing a common information space.
- a need was expressed for a united public procurement for new orphan drugs and collaboration in research across EU countries.

Challenges in Rare Diseases Field:

- Identified challenges include information accessibility, education, lack of financial support for Centres of Expertise, coordination, data collection efficiency, and inter-ministerial cooperation.
- There is a need to fundamentally rethink rare disease education and healthcare workforce,
- Actions should be aimed at shortening the path to diagnosis (called the diagnostic odyssey) and development of new therapies, stimulating multi-

stakeholder engagement and clinical trials development across the whole spectrum from students to generalists, specialists and experts, to engage and empower people living with rare diseases their families.

- The need to expand strategies and plans to develop diagnostics and care for patients with rare diseases was emphasized. This framework should include comprehensive patient care at a highly specialized center: testing and diagnostic capabilities, access to the most modern forms of treatment and qualified medical staff.

Genetic Testing and Certification:

- A need was expressed for clear legal regulations, certification of genetic laboratories, reimbursement for advanced testing, and qualified personnel.
- It is very important to be able to perform newborn screening tests for diseases

Comprehensive Medical Care and Education:

- Advocating for ensuring access to comprehensive medical care, education programs for healthcare professionals, and reliable information sources.
- Advocates also access to care, including primary care and new technologies or telemedicine, and partner strategically with patients and healthcare organizations while growing impact assessment method.
- Access to consistent quality data can support industry engagement,
- The capacity to conduct research and introduce new products technology in RD therapy must be strengthened, enhancing the ability to share relevant research on rare diseases by creating common resources and validated analytical tools,
- Development plans for artificial intelligence (AI) shorten the time needed to make an accurate diagnosis, reduce diagnosis costs as well as patient treatment costs, thereby improving treatment effectiveness. Solutions based on artificial intelligence tools are monitored in relation to personal data from healthcare.
- The introduction of new drugs involves underdevelopment of unmet needs, inequities in the availability and affordability of treatments, and inadequate adoption full range of scientific and technological developments, as discussed in the previous presentation.

Legal Improvements and Social Solidarity:

- A need was emphasized for legal improvements related to rare diseases and the removal of barriers hindering access to education and the labor market.
- The importance of building social solidarity around people with rare diseases was stressed.

EU Programs and UC Participation:

- Despite progress since 2006, under-represented countries (UCs) still face challenges in participating in European and international R&I landscapes.
- UCs often assume subordinate roles and have limited participation in activities beyond Joint Transnational Calls (JTCs).

- The prioritization and allocation of grants must be clear, equitable and transparent to all EU 13 stakeholders.

7. Next actions

The upcoming final year of the EJP RD programme will take stock of what has been achieved so far but will also contribute to defining new directions for action in the field of rare diseases.

Proposed Future Actions Based on Workshop Sessions:

Enhance Alignment with EJP RD and beyond:

- Foster ongoing collaboration and alignment between national rare disease (RD) strategies and the activities of the European Joint Programme on Rare Diseases (EJP RD).
- Establish mechanisms for regular follow-up analyses to ensure continuous alignment and adaptation to evolving EJP RD initiatives.

Strengthen National Mirror Groups (NMGs):

- Encourage the establishment and strengthening of National Mirror Groups across EU-13 countries to enhance coordination and support for rare disease initiatives.
- Share best practices and success stories from countries like Lithuania and Estonia to inspire and guide the development of NMGs in other nations.

Facilitate Transition to European RD Strategies:

- Facilitate a seamless transition from national to European RD strategies, acknowledging the specific needs and barriers of EU-13 countries.
- Encourage knowledge-sharing sessions where EU-15 countries can provide insights and support to EU-13 countries in aligning their strategies with European standards.

Address Education Needs at All Levels:

- Emphasize the importance of education in the rare disease context at all levels, from early childhood to lifelong learning.
- Develop educational programs targeting patients, their families, medical professionals, and the broader community to improve awareness, understanding, and early diagnosis of rare diseases.

Invest in Research Infrastructures:

- Allocate resources to strengthen research infrastructures that contribute to improved diagnosis and translation of research findings into clinical practice.
- Explore the integration of artificial intelligence in rare disease diagnosis, ensuring adherence to safety standards and ethical considerations.

Support Clinical Research and Orphan Product Development:

- Address challenges and leverage opportunities for EU-13 countries in clinical research and orphan medicinal product development.
- Encourage collaboration and knowledge exchange between countries facing similar challenges, with a focus on diseases like Epidermolysis Bullosa.

Explore Multi-Center Clinical Trials:

- Explore the potential benefits and challenges of multi-center (multinational) clinical trials to provide equal access to reimbursement therapy.
- Consider the feasibility and ethical aspects of compassionate use as an alternative approach in clinical trial frameworks.

Continued Panel Discussions and Recommendations:

- Organize regular panel discussions to explore and address emerging challenges in rare disease strategies, clinical research, and patient care.
- Develop actionable recommendations based on panel discussions to guide policymakers, healthcare professionals, and stakeholders in implementing effective strategies.

Periodic Workshops for Ongoing Collaboration:

- Organize periodic workshops to maintain the momentum of collaboration and information-sharing among EU-13 and EU-15 countries.
- Focus on evolving challenges and advancements in rare disease research and healthcare to ensure continuous improvement and adaptation of strategies.

Monitor and Evaluate Progress:

- Establish a system for continuous monitoring and evaluation of the progress made in implementing the proposed future actions.
- Use feedback from stakeholders and outcomes of the workshops to refine strategies and address evolving needs in the rare disease landscape.

These proposed actions aim to build on the insights and discussions from the workshop sessions, fostering collaboration, addressing challenges, and advancing strategies for improved outcomes in the rare disease field, particularly in EU-13 countries.