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Joint Action to Support the eHealth Network

REPORT

on

Elements to be Taken Into Consideration for Updating the PARENT Joint Action Guidelines for Patient Registries

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LIST OF ABBREVIATIONS

ACRONYM	DEFINITION
CEF	CONNECTING EUROPE FACILITY
CPMS	CLINICAL PATIENT MANAGEMENT SYSTEM
CSIRT	COMPUTER SECURITY INCIDENT RESPONSE TEAMS
DPIA	DATA PROTECTION IMPACT ASSESSMENT
eHDSI	EHEALTH DIGITAL SERVICE INFRASTRUCTURE
EHN	EHEALTH NETWORK
eIDAS	ELECTRONIC IDENTIFICATION AND TRUST SERVICES
EMA	EUROPEAN MEDICINES AGENCY
ERN	EUROPEAN REFERENCE NETWORK
EUNetHTA	EUROPEAN NETWORK FOR HEALTH TECHNOLOGY ASSESSMENT
FAIR	FINDABLE, ACCESSIBLE, INTEROPERABLE, AND RE-USABLE
GDPR	GENERAL DATA PROTECTION REGULATION
HTA	HEALTH TECHNOLOGY ASSESSMENT
JAseHN	JOINT ACTION TO SUPPORT THE EHEALTH NETWORK
JRC	JOINT RESEARCH CENTRE
NIS Directive	DIRECTIVE ON SECURITY OF NETWORK AND INFORMATION SYSTEMS
PARENT JA	CROSS-BORDER PATIENT REGISTRIES INITIATIVE JOINT ACTION
PLEG	POST-LAUNCH EVIDENCE GENERATION
PPRL	PRIVACY PRESERVING RECORD LINKAGE
PR	PATIENT REGISTRIES
RD	RARE DISEASES
ReIF	REFINED EHEALTH INTEROPERABILITY FRAMEWORK
RoR	REGISTRY OF REGISTRIES

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1. Executive Summary

This document is the report from Task 5.3.3 of the Joint Action supporting the eHealth Network (JAseHN) Task 5.3.3, responsible for reviewing the patient registries (PR) guidelines.

It is the third deliverable of the JAseHN work package 5.3, responsible for revising and, where appropriate, updating three sets of guidelines presented to the eHN: the guidelines for a common dataset for (a) Patient Summary and (b) ePrescriptions for the electronic exchange under the cross-border directive 2011/24/EU, and (c) the Methodological guidelines and recommendations for efficient and rational governance of patient registries drafted by the PARENT Joint Action.

For the Patient Summary guidelines (T5.3.1) and the ePrescription guidelines (T5.3.2), the updates validated by the eHN in its meeting of 21 November 2016, reflect the move from pilot status to readiness for mass deployment under CEF using the eHealth Digital Service Infrastructure.

The aforementioned PARENT Methodological guidelines on PR, subject matter of the present report, were submitted to the eighth eHN meeting in November 2015, who endorsed a series of recommendations on the use of knowledge gathered through the PARENT Joint Action in place of formally adopting the guidelines as such. Therefore, JASeHN Task 5.3.3 has focused on the progress made with the recommendations[1] and on relevant impacting developments from the past couple of years. The companion JAseHN Task 6.1.3 has carried out a survey into the application and use of the guidelines across Member States. In parallel with this, a multi-stakeholder workshop was held on 1 February 2018, with the following objectives:

- to give the stakeholders a common understanding of the eHealth Network and the JAseHN Joint Action
- to hear of progress on the recommendations from the PR guidelines and the current and future plans in the area of patient registries, ERNs, etc.
- to consider the impacting legislation and supporting instruments that have come about since the publication of the PARENT PR guidelines in 2015
- to advise on the next steps and propose recommendations for future action.

The aforementioned workshop heard of significant developments regarding the application of the guidelines to support Health Technology Assessment (HTA) with the development of the Post-Launch Evidence Generation (PLEG) tool, together with proposals from the European Medicines Agency (EMA) and other groups to strengthen observational analysis and the quality of data collection.

The workshop also heard about the many developments in the field of rare diseases with the RD Joint Action, the development and selection of European Reference Networks and associated supporting systems.

[1] https://ec.europa.eu/health//sites/health/files/ehealth/docs/ev_20151123_co05_en.pdf

In the field of eHealth, the cross-border activities for Patient Summary and ePrescription have continued. These have been assessing the implications of new legislative instruments that have come about such as the General Data Protection Regulation, the eIDAS regulation and the Networking and Information Security (NIS) Directive. Discussions within JAseHN had assessed the relevance of these to patient registries, and where this might require an update to the registry guidelines. The development of the Refined eHealth Interoperability Framework (ReIF) has also provided a structured basis for planning systems development and implementation.

The strong message from the 1 February multi-stakeholder workshop was rather than attempting to refresh the 200-page guidelines, it would be better to highlight the progress made, to document those things that have changed, to discuss the implications of the activities of each stakeholder group and, most importantly, to consider a refreshed set of recommendations that would be able to bring together the fields of activity to mutual advantage.

Accordingly, the structure for this report is as follows:

- The background section (2) reprises the context and the recommendations made in 2015
- The current position section (3, 4) – in two parts - describes progress made since then on the recommendations and more generally in the field of patient registries and rare diseases
- The impact section (5) gives an overview of the legislative changes since 2015 and provides a set of pointers and questions relevant to patient registries
- The emerging findings section (6) summarises the position on the 2015 recommendations, identifies important aspects to be addressed, some of which are unresolved from previous work and some of which are new. A significant issue is the shared need for sustainability. Many current facilities are funded on a short-term basis only, and often in a standalone fashion, hence not taking advantage of the synergies between the various initiatives. Given the need to demonstrate trust and confidence, there are shared needs to balance transparency and defensibility in turn linked to assurance of data quality and hence usefulness.
- Together, the progress and the issues provide a set of Opportunities for the future and these lead into a revised set of recommendations for consideration by the eHN and for DG Santé to share with equivalent groups for patient registries. A number of these relate to the development, implementation and use of standards to support interoperability and compatibility.

Alongside these specific recommendations, there will be broader opportunities for continued working both at the policy level and for shared activities between the respective Joint Action tasks.

2. Background

2.1. Introduction

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2.2. Cross-Border Directive

This chapter summarises the context of PARENT Joint Action and its outputs. The following chapters describe developments since November 2015 in the field of patient registries and rare diseases.

The policy context was set by the DIRECTIVE 2011/24/EU OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 9 March 2011 on the application of patients' rights in cross-border healthcare. CHAPTER IV: COOPERATION IN HEALTHCARE describes a number of areas for co-operation between Member States:

Article 10: Mutual assistance and cooperation

Article 11: Recognition of prescriptions (addressing also medical devices);

Article 12: European Reference Networks;

Article 13: Rare Diseases

Article 14: eHealth for the purposes of safety and quality of care, continuity of care, and health research.

Article 15: Co-operation on Health Technology Assessment.

The combination of the eHN work on 14 and implementing DSIs which recognize 11 sits alongside the activities under 12, 13 and 15 described here.

2.3. PARENT Joint Action

The main objective of PARENT Joint Action was to improve the cross-border availability of health data for public health and research. PARENT built its work from the starting point that the set objective can truly be achieved only by building on a digital infrastructure for collection, processing and utilisation of health data. At present, the majority of patient registries in the EU is still at a very early stage in utilising IT solutions. Hence the engagement

of MS – through the eHN- in promoting and supporting the goal of patient registries as a part of health data infrastructures was seen as decisive.

PARENT deliverables were developed around three central questions/subjects:

- where are the data: an answer was given through the Registry of Registries (RoR)
- are the data reliable?
- are the data accessible?

The process of setting up patient registries and defining common guidelines respond to 3 EU policy objectives:

- to enhance cooperation between health systems (interoperable patient registries on the eHealth agenda)
- to give EU citizens access to better and safer healthcare (PR as tools for ERNs and rare disease services/research) and
- to contribute to innovative, efficient and sustainable health systems (strengthen usefulness of PR for HTA-based patient safety).

PARENT defined a patient registry as "an organised system that collects, analyses, and disseminates the data and information on a group of people defined by a particular disease, condition, exposure, or health-related service, and that serves a predetermined scientific, clinical or/and public health (policy) purposes. "

The PARENT Joint Action ran from 2012 to April 2015 and was extended until November 2015. The extension enabled PARENT to collaborate with the eHealth community through EXPAND (to include PARENT assets in the registry) and to collect more feedback on the Guidelines from eHN MS in order to ensure the Guidelines' suitability with MS' needs.

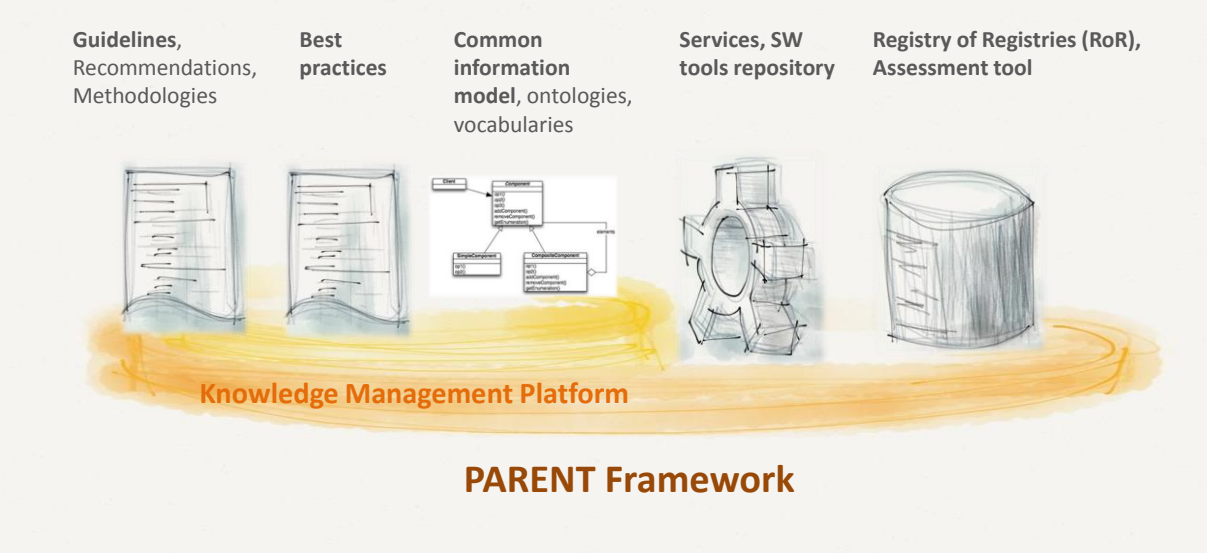

Figure 1-PARENT Framework

The deliverables from PARENT were:

- Registry of registries, which at project termination contained 150 registries http://www.parent-ror.eu
- Methodological Guidelines and Recommendations for efficient and rational governance of patient registries http://patientregistries.eu/deliverables or http://parent-wiki.nijz.si
- Producing IT-based advance knowledge management tools: these tools are looking at the datasets used in the registries and allowing assessment of various levels of registry cross-border interoperability
- Patient Registries as support mechanism of Cross-border Healthcare Directive implementation and Future Policy Actions (Report, incl. analysis of possibilities for aligning NCPeH architecture with cross-border registries architecture & collaboration with the HTA community)
- Sustainability of cross-border collaboration on secondary use of registry data. Business models Analysis Report (Report, incl. description of PARENT Framework Governance in the eHDSI environment).

PARENT created the Guidelines to provide practical and 'hands on' advice to set up and manage digitally enabled PRs as well as to enable their secondary use for public health policy and research, within the EU data protection framework.

The most important features of the registries, which could improve or discourage semantic interoperability, are coding systems, standards and data model used. To increase the usefulness of the data collected in the registries, it is necessary to ensure that registries are interoperable and of high quality, in terms of their comprehensiveness, collection of important data, and monitoring of relevant patient outcomes. The assessment tool which is part of the PARENT pilot RoR can provide a useful indication of all levels of registry interoperability.

2.4. eHealth Network 2015 Recommendations

The guidelines were introduced to the eHN meeting held in May 2015 in Riga. MS experts were invited to contribute to the PARENT workshop by sending their recommendation or comments on a specific topic before the workshop. There was further discussion at the eHN meeting in November 2015. Whilst the eHN did not formally approve the guidelines produced by PARENT, they encouraged their use by endorsing the following recommendations, some allocated to Member States, some to the European Commission and some to both.

Member States and the Commission agreed to:

- promote the inclusion of further registries in the RoR;
- support the dissemination and uptake of PARENT Guidelines;
- encourage collaboration between the registries and other stakeholders;

The European Commission agreed to:

- explore mechanisms for regular updating of the Guidelines;

- integrate PARENT JA deliverables with the work in which the JRC (Joint Research Centre) is currently engaged;
- bring together the experiences of the registries already set up at EU level;
- pilot the PARENT deliverables on some test cases;
- explore the usefulness of a specific body on health data interoperability

Registry holders and Member States were encouraged to:

- improve registry quality and interoperability by following and implementing the PARENT Guidelines;
- demonstrate the importance of registry data for evidence-based policy making;
- increase patients' awareness of the importance of high-quality registry data and encourage their involvement in the generation and use of data;
- share the national legislations, plans and strategies concerning the areas of registries, eHealth/Electronic Health Records, Rare Diseases, HTA and potentially European Reference Networks.

3. Update following PARENT

3.1. Registry of Registries (RoR)

After the PARENT Joint Action ended, some of its key deliverables (methodological guidelines, best practices, list of common datasets, Registry of Registries, assessment tools) were disseminated, implemented or developed and re-used through various activities and actors on EU level: Health Technology Assessment Joint Action (HTA JA) - evidence generation; the European Medicine Agency (EMA) - patient registry initiative to optimise the use of registries in supporting medicines authorisations; the Joint Research Centre – building the European Rare Diseases Platform including the European Rare Disease Registry Infrastructure and European Reference Networks (ERN) - Clinical Patient Management System. The 1st February workshop heard of the many activities that have followed from, and built upon, the work of the PARENT Joint Action. These are outlined in this and the following chapter.

One of PARENT outputs was the Registry of Registries. This now has over 200 entries (see www.patientregistries.eu). This is not just a "yellow pages" list, but additionally provides information on patient registry data reliability. The metadata of RoR cover fine-grained information on quality parameters, data sharing and data linkage preparedness and procedures, subject identifier type and speed of response to cross-border data requests.

The RoR functions in conjunction with the Assessment Tool, i.e. data entry on any participant registry and its corresponding interoperability assessment can be performed simultaneously. Part of RoR v.2 is integrated with the Guidelines content. The Assessment tool supports patient registry development by giving improvement recommendations to registry holders. Through reviewing completeness of data in RoR users receive a comprehensive assessment of registry status & qualities, accuracy of information (periodical

update and confirmation), registry quality characteristics, and registry interoperability characteristics.

The workshop on 1 February was an opportunity to highlight other areas of good practice.

The European Society of Cardiology has three types of registries in the clinical cardiology field and two different prevention registries (*detail see:* https://www.escardio.org/Research/Registries-&-surveys/Observational-registry-programme/registry-overview). In total 20 registries have been created since 2010, which form part of a continuous program. The adherence by the patient is on a voluntary basis. When starting up a registry one has to define how to use data, what content, etc. which makes it difficult to broaden the scope afterwards, also in view of the GDPR.

3.2. Health Technology Assessment (HTA) and EUnetHTA Joint Action

The Directive 2011/24/EU on the application of patients' rights in cross-border healthcare stipulates (Article 15) that the Union shall support and facilitate co-operation between national authorities or bodies responsible for health technology assessment designated by the Member States. According to the Implementing Decision, the Health Technology Assessment (HTA) Network is to be supported by a scientific and technical cooperation to meet the objectives of the European cooperation on HTA as per Article 15 of the Directive. The EUnetHTA Joint Actions have performed the scientific and technical cooperation of the HTA Network.

The three successive EUnetHTA Joint Actions - the first one covering the period 2010-2012, the second one 2012-2015, and the currently ongoing third one for the period 2016-2020 - were established to create an effective and sustainable network for HTA across Europe, to work together to help developing reliable, timely, transparent and transferable information to contribute to HTAs in European countries. EUnetHTA supports collaboration between European HTA organisations that brings added value at the European, national and regional level through facilitating efficient use of resources available for HTA creating a sustainable system of HTA knowledge sharing and promoting good practice in HTA methods and processes.

The first EUnetHTA JA refined the collaboration structure and tools with attention to global developments in the field. The strategic objectives of the EUnetHTA JA2 were to:

- strengthen the practical application of tools and approaches to cross-border HTA collaboration
- bring collaboration to a higher level resulting in better understanding for the Commission and Member States of the ways to establish a sustainable structure for HTA in the EU
- develop a general strategy, principles and an implementation proposal for a sustainable European HTA collaboration according to the requirements of Article 15 of the Directive for cross-border healthcare.

The current EUnetHTA JA3 started in 2016 and comprises over 70 institutes. It aims to be an effective and sustainable network for Health Technology Assessment (HTA) across Europe.

Early engagement took place between PARENT and the HTA Network, at which it was agreed that registries could add to regular HTA methods in relation to real life safety and clinical effectiveness, rare events as well as long term data, and can help in describing the population of interest and in collecting data for later assessments.

There are important reasons why HTA standards should be used for registries:

- Patient registries are a source of real-world data (RWD) for evidence generation for HTA
- The value of RWD in measuring a technology's *effectiveness vs efficacy,* e.g. how well a technology performs in the real population in less controlled environment (routine health care practice), as opposed to measuring performance in a carefully selected settings (RCT, Randomized Controlled Trial)
- RWD from registries is used more extensively than recognised in literature and for more advanced inputs into the HTA than published.

One of the currently ongoing EUnetHTA JA 3's sub-activities (strand B) of its work package 5 (Life cycle approach to improve Evidence Generation) relates to Patient Registries: "Post-Launch Evidence Generation (PLEG) and Registries". It comprises two main topics: running pilots and put in place a PLEG-tool, and aims to produce specific HTA targeted guidelines to improve registries used for assessment with two types of pilot:

- "Full" pilots initiated by HTA bodies, following the identification of evidence gaps in an HTA report. The pilots will consist in producing a common research question and minimum data set for registries, and, if possible, a definition of a core common protocol.
- "Collaborative" pilots initiated by other bodies/projects. Involvement will mainly consist in complementing the initial request with HTA bodies' requirements.

The PLEG tool aims to ensure that good quality data is collected, and to enable later best use of data gathered from PLEG, especially registries, all in order to make permanent PLEG collaboration operational.

The EC has recently published a communication informing about the European Commission's proposal to reinforce cooperation amongst Member States in the area of HTA[2].

By way of example, the NHS Institute for Clinical Excellence (NICE) is a HTA agency. Like colleagues in other countries, they need many data sources, so require collaboration with other countries. They are trying to develop patient registries to inform their observational data unit; they run projects commissioning for evaluation programme by NHS England
NICE have recently become involved with the PLEG tool looking at drug intervention, in

[2] http://europa.eu/rapid/press-release_IP-18-486_en.htm

conjunction with the regulator (MHRA). They are hoping to use renal registry. NICOR is a PLEG pilot

3.3. European Medicines Agency (EMA)

EMA describe patient registries as "organised systems that use observational methods to collect uniform data on a population defined by a particular disease, condition, or exposure, and that is followed over time". EMA believe that high quality patient registries can make valuable contributions to the evaluation and monitoring of medicines for public health benefit, especially in relation to their safety and notwithstanding that most registries were not established for this purpose.

Regulators and pharmaceutical companies currently face a number of challenges in using existing registries or establishing new ones to support medicines evaluations during the marketing authorisation process, amongst which the lack of: co-ordination between ongoing initiatives at national and international levels, harmonised protocols, scientific methods and data structures, data sharing and transparency and long-term sustainability of registries.

These factors have led to under-use of existing patient registries, inefficiency when registries are used, non-useable registries, and duplication of efforts. To address these problems, and given the importance of harnessing real world data to support risk monitoring of medicinal products, the EMA announced an initiative to create a European Union-wide framework on patient registries, facilitating collaboration between registry coordinators and potential users of registry[3] data. This initiative stated that „Any new registry should be based on standard methodological approaches including standard core components of a protocol and core data elements, such as those developed by the PARENT JA.

4. Rare diseases

4.1. Rare diseases – what are they?

Rare diseases are defined in this context as life-threatening or chronically debilitating diseases – mostly inherited – that affect so few people that combined efforts are needed to:

- reduce the number of people impacted by such diseases
- prevent newborns and young children dying from them
- preserve sufferers' quality of life and socio-economic potential.

In EU countries, any disease affecting fewer than 5 people in 10 000 is considered rare. That number may seem small, but it translates into approximately 246 000 people throughout the EU's 28-member countries. Most patients suffer from even rarer diseases affecting 1 person in 100 000 or more. It is estimated that today in the EU, 5-8000 distinct rare diseases affect 6-8% of the population – between 27 and 36 million people.

[3] http://www.ema.europa.eu/docs/en_GB/document_library/Other/2015/10/WC500195576.pdf

Patient registries are particularly important because they provide essential data sources to inform the development, approval and reimbursement of orphan drugs to combat rare diseases.

Patient registries and databases constitute key instruments to develop clinical research in the field of rare diseases, to improve patient care and healthcare planning. They are the only way to pool data in order to achieve a sufficient sample size for epidemiological and/or clinical research. They are vital to assess the feasibility of clinical trials, to facilitate the planning of appropriate clinical trials and to support the enrolment of patients as well as for the post-marketing surveillance of orphan medicinal products. The creation of a registry can be a powerful tool to create and structure networks of experts, whether they are European Reference Networks of Centres of Expertise or national expert networks for RD. In either case, the experts and centres of expertise involved are a primary source of data for registries.

The EC is helping to pool scarce resources that are currently fragmented across individual EU countries. Specific measures include:

- improving recognition and visibility of rare diseases
- ensuring that rare diseases are adequately coded and traceable in all health information systems
- supporting national plans for rare diseases in EU member countries
- strengthening European-level cooperation and coordination, e.g. through the RD Joint Action described in the following sub-section
- creating European reference networks linking centres of expertise and professionals in different countries to share knowledge and identify where patients should go when expertise is unavailable in their home country
- encouraging more research into rare diseases
- evaluating current population screening practices
- supporting rare diseases registries and providing a European Platform for rare diseases registration.

The EU has recommended that Member States should consider supporting specific disease information networks and, on the other hand, for epidemiological purposes, registries and databases, whilst being aware of an independent governance. (Council Recommendation on an action in the field of rare diseases (2009/C 151/02)javascript:void(0).

The strategical objective of the European Commission is the creation of a **European Platform on Rare Diseases Registration** providing common services and tools for the existing (and future) rare diseases registries in the European Union.

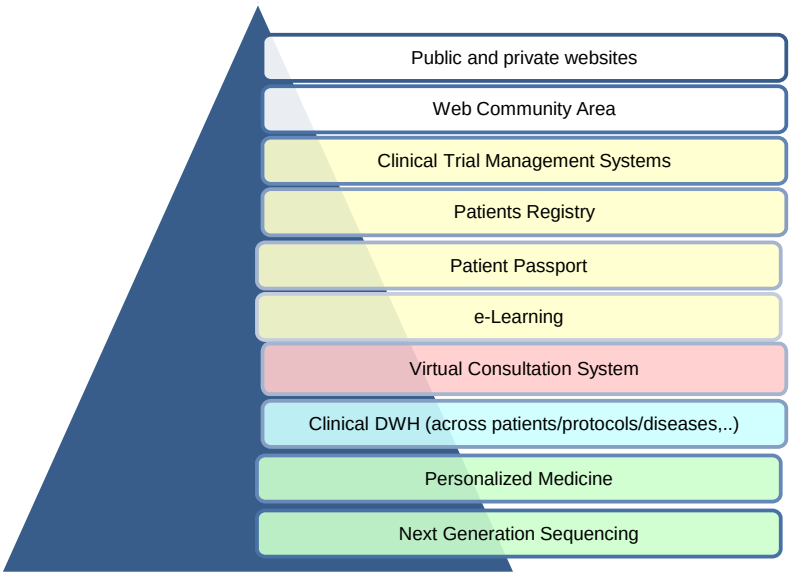

Figure 2-Functions of a disease network

A list of the existing 600 rare diseases registries in Europe can be found in the Orphanet Report - Disease Registries in Europe - January 2013. No uniform, accepted standards govern the collection, organisation, or availability of these data, and often more than one registry exists for the same rare disease. At the same time, one estimate is that registries exist for only 20% of rare diseases.

4.2 RD Action

RD Action was established to consolidate and formalise interactions to-date between the RD and eHealth communities (especially the JAs). An Exploratory Paper on Convergence of Rare Disease and eHealth initiatives took an initial focus on Networks in RD field, i.e. ERNs, considering how to optimise the eHealth DSIs of CEF for rare diseases. The registries issue was highlighted from the start and shelved a little, as it seemed to move from the eHN radar.

RD-ACTION works towards an integrated, European approach to the challenges faced by the rare disease community. By supporting the development of European and national policies, RD-ACTION brings together efforts to improve knowledge on rare diseases and orphan drugs and support the rare disease community. The current third Joint Action for rare diseases, called RD-Action (follow-up of the former Orphanet and EUCERD Joint Actions), was launched in 2015, covers 3 years and has 3 main objectives:

- contribute to the implementation, by Member States, of the recommendations of the EC Panel in relation to policies on rare diseases,
- support the development of Orphanet and make it sustainable
- help Member States to introduce the ORPHA code in their health systems to make rare diseases visible.

In complex rare diseases, a patient may have the same (apparent) genetic mutation / anomaly but exhibit very different clinical presentations, with varying severity and prognosis. To capture and understand these variations, and translate this knowledge a) to better diagnostics and care for the patient under review, and b) to drive forwards the pace of knowledge and understanding for the field at large, it is often necessary to capture detailed

phenotypic descriptions. Given the scarcity and thus value of data in the rare disease and specialised healthcare field, it is important to optimise the utility of this clinical information, in terms of immediate, one-to-one patient benefit but also re-use, for instance by searching databases and computing similarity: the best way to do this is to use an agreed ontology for capturing phenotypes. The Human Phenotype Ontology (HPO) is considered the most appropriate ontology for capturing the clinical presentation of rare diseases.

In view of the considerations above, the following are hereby recommended:

1. ERNs and their constituent HCPs should promote use of the HPO as the most appropriate ontology for capturing phenotypic descriptions in patients with a suspected rare disease or those requiring highly specialised procedures/techniques in which there is a need to build an evidence base.
2. ERNs -and particularly their common systems for exchanging patient data, such as the Clinical Patient Management System- should consider how best to use HPO, depending on the type of data collected:
3. When and where possible, ERN communities should seek to evaluate and improve the relevance of HPO terms in their particular thematic grouping/subdomain, by liaising with the HPO development team and considering the organisation of a dedicated workshop for these purposes.

Rare Diseases are most in demand of registration of data and the interoperability of those data. Because of the rareness, there is a huge necessity to link data and have the patient's voice in it as well. The Task Force put in place by RD Action has investigated the synergies between the eHealth and the Rare Disease activities and started the collaboration with those different communities and stakeholders. Four key tools/approaches were highlighted as enablers for optimising the value of data in the ERN community:

- Coding rare diseases within ERNs
- Capture phenotypic information in ERNs
- FAIR-ify data: i.e. data should be Findable, Accessible, Interoperable, and Re-usable - ERNs and their constituent HCPs should stimulate working on local data quality;
- Ensure pseudonymisation of demographic and patient data, by applying a solution supported by the international community Privacy Preserving Record Linkage (PPRL)

Hence, the strategic issues with regard to Patient Registries and updating the relevant guidelines are to:

- work out concrete use cases in the vast area of PR (many actors involved, vast number of fragmented PR, capture the main issues)
- once use case(s) has(ve) been defined, engage the relevant stakeholders and beneficiaries
- update the content accordingly and ensure sustainability of PARENT deliverables.

Several cite the desire to link data from biobanks & registries. Many ERNs will deliver an annual Inventory of existing registries & biobanks in their field and update it each year. Some set very specific goals e.g. 10% increase in the number of samples and data for research.

4.3. European Reference Networks (ERNs)

ERNs are networks that group rare diseases in thematic networks with the aim to create a critical mass and connect the patient to the clinician by means of a cross-border cooperation platform between specialists, used for the diagnosis and treatment of rare or low prevalence complex diseases. In total 24 ERN have been approved, involving more than 900 highly specialised healthcare units from over 300 hospitals in 26 EU countries. They are not silos, however. For instance; all metabolic disease areas work together. All face sustainability issues. The aim is for a link with HTA for expensive drugs, but this is not yet in place.

The ERN Coordinators Group has defined a number of activities allocated to different work groups. The group has produced the following documents (*www.metab.ern-net.eu*)

- CONFLICT OF INTERESTS AND CODE OF CONDUCTS
- CONSENSUS DOCUMENT ON NEW ERN MEMBERSHIPS
- MONITORING OF ERN ACTIVITIES
- MetabERN: ERN on HEREDITARY METABOLIC DISEASES

ERNs are keen users of technology and are incubators for the development of digital services for the provision of virtual healthcare: Telemedicine, Virtual Consultation, Virtual Emergency Prescription, RD Passport, Registries, Clinical Data bases, Interactive website, E-learning / teaching. ERN activities span the care cycle, as illustrated below.

Figure 3-Aspects of clinical pathway

The ERNs rely on two technological tools to support such provision of virtual healthcare: a virtual consultation platform (CPMS) and patient registries.

The health professionals participating in the ERN use the Software as a Service "Clinical Patient Management System (CPMS)" as a tool for collaboration and virtual consultation with regard to diagnosis and treatment of patients. It will be tested in 120 real cases starting February 2018. At present, five ERN registries have been funded by the EC through

CHAFEA (MetabERN, ERKNET, ERN PaedCan, ERN Lung, EndoERN), but the number is to be extended and their interoperability to be ensured with the aim to evolve towards an EU Registry for Rare Diseases. They need ehealth modules to help align the 600+ metabolic registries already in place. This would also be an opportunity to test the PARENT deliverables applicability and suitability for supporting the RD community.

4.4. Joint Research Centre

As the European Commission's science and knowledge service, the Joint Research Centre (JRC) supports EU policies with independent scientific evidence throughout the whole policy cycle[4], and has the mission to:

- create, manage and make sense of knowledge and develop innovative tools and make them available to policy makers
- anticipate emerging issues that need to be addressed at EU level and understand policy environments
- develop innovative tools and make them available to policy makers
- share know-how with EU countries, the scientific community and international partners
- contribute to the overall objective of Horizon 2020
- collaborate with over a thousand organisations worldwide whose scientists have access to many JRC facilities through various collaboration agreements

The JRC has been working closely with DG Santé on Rare Diseases to develop the European Platform on Rare Diseases Registration (EU RD Platform) in order to tackle the issue of fragmentation of data regarding rare disease patients. The first practical instrument aiming for an increased interoperability of the data registries which was released by the EU RD Platform is the "Set of Common Data Elements for Rare Diseases Registration"[5]. It defines the minimum data elements to be registered by all rare diseases registries across Europe and provides instructions on how and in which format each data element should be registered.

The document describes the 16 data elements considered to be essential to enable further research. They refer to patient's personal data, diagnosis, disease history and care pathway, as well as information to be provided for research purposes. All existing and new data registries across Europe are recommended to use this standard as the basis for their data collection activities. The standard was produced by a Working Group coordinated by the JRC and composed of experts from EU projects working on common data sets: EUCERD Joint Action, EPIRARE and RD-Connect.

[4] https://ec.europa.eu/info/departments/joint-research-centre_en#responsibilities
[5] See: https://ec.europa.eu/jrc/en/news/pooling-data-combat-rare-diseases

5. Contextual Changes Impacting Patient Registries

In the past three years, several important items of legislation have been adopted that are designed to improve trust, privacy and security. Each is relevant to patient registries and each has implications for those who build and operate registries. This chapter discusses the General Data Protection Regulation, the eIDAS Regulation and the Networking and Information Systems (NIS) Directive.

5.1. GDPR

Regulation 2016/679 on the "protection of natural persons with regard to the processing of personal data and on the free movement of such data" (General Data Protection) was adopted on 27 April 2016. It repeals Directive 1995/46 and is applicable from 25 May 2018. Any new processing shall comply with the GDPR. Ongoing processing which has been authorised under the repealed Directive 1995/46/EC remains valid. Processing under the repealed Directive shall comply with the new GDPR within two years from 25 May 2018.

One of the objectives for the Regulation is consistent and homogenous application of the rules, but Member States are allowed to maintain or introduce national provisions to further specify the application of the Regulation regarding processing of personal data for compliance with a legal obligation, for the performance of a task carried out in the public interest or in the exercise of official authority vested in the controller. This could leave room for national rules that are more specific for the processing of personal data in the public sector.

In most digital transactions, there are risks regarding the processing and storage of personal data that might lead to the accidental or unlawful destruction, loss, alteration, unauthorised disclosure of such data. GDPR aims to address these situations by introducing stricter rules for data controllers and processors and new rights for data subjects regarding personal data.

There are no fundamental changes to Directive of 1995/46; GDPR regulates data controllers and data processors acting in the public and private sectors for profit and not-for-profit purposes and it regulates sensitive personal data such as health data, genetic data and biometric data because of the risks regarding the rights and freedoms of the data subject. More specifically for patient registries, it regulates scientific research as a special kind of personal data processing.

However, the GDPR introduces several changes and introduces new procedures. GDPR introduces general rules applying to any kind of personal data processing and specific rules applying to the processing of special categories of personal data such as health data. For instance, GDPR adopts an (innovative) risk-based approach intended to facilitate the case-by-case identification of data protection issues and recognises several new data protection principles. It redefines terms used in data protection and introduces new data protection procedures. The GDPR Principles are:

- *Lawfulness, fairness and transparency* – data shall be processed lawfully, fairly and in a transparent manner in relation to the data subject;
- *Purpose limitation* – data shall be collected for specified, explicit and legitimate purposes and not further processed in a way incompatible with those purposes;
- *Data minimisation* – data shall be processed in a manner that is adequate, relevant and limited to what is necessary regarding its purposes;
- *Accuracy* – data shall be accurate and up to date regarding the purposes for which they are processed; inaccurate data shall be erased or rectified without delay;
- *Storage limitation* – data shall be kept in a form which permits identification of data subjects for no longer than is necessary for the purposes for which the personal data are kept;
- *Integrity and confidentiality** – data shall be processed in a manner that ensures appropriate security of the personal data;
- *Accountability* - data controller shall be responsible for, and be able to demonstrate compliance with the general principles of data processing under the GDPR

Table 1-Principles of Data Protection

GDPR advocates Privacy by Design. The Data Controller shall implement appropriate technical and organisational measures for ensuring that, by default, only personal data which are necessary for each specific purpose of the processing are processed. Further, the Data Controller shall implement appropriate technical and organisational measures (e.g. *pseudonymisation* and *data minimisation*) in order to meet the requirements of the GDPR and protect the rights of data subjects.

The data subject is entitled to receive the personal data concerning them, in a 'commonly usable and machine-readable format' and have the right to transmit that data to another controller (Data Portability principle)". Data subjects' right of access includes obtaining from the data controller confirmation as to whether or not personal data concerning them is being processed, where and for what purpose. Data subjects also have the Right to be Forgotten (a.k.a. Data Erasure) which entitles the data subject to have the data controller erase his/her personal data, cease further dissemination of the data, and potentially have third parties halt processing of the data. The conditions for erasure, as outlined in Article 17 include the data no longer being relevant to original purposes for processing, or a data subject's withdrawing consent.

The GDPR has strengthened the conditions for consent whereby the request for consent must be in a clear, intelligible and easily accessible form whereby the purpose for data processing is clearly described. Consent is any freely given, specific, informed and unambiguous indication of the data subject's wishes by which she/he, by a statement or by a clear affirmative action, signifies an agreement to the processing of personal data relating to her/him. Consent has been specified as a legal basis only in when there is no uncertainty about the scope of the activities agreed by the data subject and the form of consent (statement or clear affirmative action). GDPR does recognise other legal basis for the purposes of informing the patients about obtaining/transferring/storing etc. of their data (e.g. national law).*

The GDPR gives a new clear definition of "health data" and sets some stricter rules for the data controller to implement the appropriate technical and organisational measures to

safeguard the protection of such data by means of a pseudonymisation process. Accordingly, "Data concerning health" is defined as all data pertaining to the health status of a data subject which reveal information relating to the past, current or future physical or mental health status of the data subject. This includes information about the natural person collected in the course of the registration for, or the provision of, health care services as referred to in Directive 2011/24/EU of the European Parliament and of the Council to that natural person. Such information might be a number, symbol or particular assigned to a natural person to uniquely identify the natural person for health purposes, information derived from the testing or examination of a body part or bodily substance, including from genetic data and biological samples or any information on, for example, a disease, disability, disease risk, medical history, clinical treatment or the physiological or biomedical state of the data subject independent of its source, for example, from a physician or other health professional, a hospital, medical device or an in vitro diagnostic test.

Pseudonymisation is the processing of personal data in such manner that the personal data can no longer be attributed to a specific data subject without the use of additional information, provided that such additional information is kept separately and is subject to technical and organisational measures to ensure that the personal data are not attributed to an identified or identifiable natural person. GDPR endorses the use of pseudonymisation as a standard data protection practice of personal data processing for scientific research purposes.

Anonymous data is information which does not relate to an identified or identifiable natural person or to personal data rendered anonymous in such a manner that the data subject is not or no longer identifiable. The GDPR does not, therefore, concern the processing of such anonymous information, including for statistical or research purposes.

The GDPR establishes a risk-based approach to data protection. According to Article 37, designating a Data Protection Officer (DPO) is mandatory where the processing is carried out by a public authority or body, except for courts acting in their judicial capacities, where the core activities of the controller or the processor consist of either processing operations which, by virtue of their nature, their scope and/or their purposes, require regular and systematic monitoring of data subjects on a large scale, where the processing concerns sensitive personal data on a large scale.

The aim of the Data Protection Impact Assessment (DPIA) is to assess the likelihood and severity of the risk regarding data subjects' rights and freedoms. A DPIA should be performed prior to data processing, and take into account a systematic description of the envisaged processing operations and the purposes of the processing, including, where applicable, the legitimate interest pursued by the controller, an assessment of the necessity and proportionality of the processing operations in relation to the purposes, an assessment of the risks to the rights and freedoms of data subjects […] and the measures envisaged to address the risks.

5.2. eIDAS

Another relevant piece of legislation is the Regulation (EU) 2014/910 - Regulation of the European Parliament and of the Council of 23 July 2014 on electronic identification and trust

services for electronic transactions in the internal market and repealing Directive 1999/93/EC.

The eIDAS Regulation, which came into force on 17 September 2014, was adopted to facilitate seamless, secure electronic interactions between businesses, citizens and public authorities across the EU. eIDAS ensures that people and businesses can use their own national electronic identification (eID) schemes to access public services in other EU countries where eIDs are available. It creates a European internal market for electronic Trust Services (TS) - namely electronic signatures (for natural persons), electronic seals (for legal persons), time stamps, electronic registered delivery service and website authentication, and to a lesser extent eDocuments - by ensuring that they will work across borders and have the same legal status as traditional paper-based processes.

In the area of the eHealth, mutual recognition of electronic identification (say who you are) and authentication (prove that you are who you say you are) is essential for making cross-border healthcare for EU citizens a reality, in a solid, safe and trusted electronic identification environment. The intended benefits are:

1. Citizens will be able to carry out secure cross-border electronic transactions moving to another Member States and take full advantage of their rights across the EU.
2. Businesses will have significant reduction in overheads - boosting profits. It can make the difference between expansion and stagnation for small and medium sized businesses.
3. Government services become more flexible and convenient, like the private sector.
4. Greener environment!

The Directive on Patients' Rights in cross-border healthcare (2011/24/EU) of the European Parliament and of the Council set up a Network of national authorities responsible for e-health (eHN). To enhance the safety and the continuity of cross-border healthcare, the network is required to produce guidelines on cross-border access to electronic health data and services, including by supporting 'common identification and authentication measures to facilitate transferability of data in cross- border healthcare'.

Mutual recognition of electronic identification and authentication is key to making cross-border healthcare for European citizens a reality. When people travel for treatment, their medical data need to be accessible in the country of treatment. That requires a solid, safe and trusted electronic identification framework.

Such framework encompasses Electronic Identification, Trust services and Electronic Documents and defines the broad array of elements including criteria, processes for establishment, supervision and conformity assessment that are necessary to allow for mutual recognition of notified national eID schemes, electronic signatures and electronic seals. The Regulation foresees enhanced supervision mechanisms for qualified trust service providers by MS as well as reporting by these mechanisms to enable the Commission and the Member States to assess their continuing conformance.

The eIDAS Regulation establishes the regime under which all trust service providers should be liable for damage caused to any natural or legal person due to failure to comply with the

obligations under this Regulation. It allows trust service providers to set limitations, under certain conditions, on the use of the services they provide and not be liable for damages arising from the use of services exceeding such limitations.

Providing a legal framework to facilitate cross-border recognition between existing national legal systems related to electronic registered delivery services is also an important enabler. The Regulation promotes IT security certification based on international standards and related evaluation methods. Processes could be facilitated by a peer review. Notification of security breaches and security risk assessments is essential with a view to providing adequate information to concerned parties in the event of a breach of security or loss of integrity.

The regulation, in its Recital 10, makes explicit reference to the provisioned eHealth Network guidelines 'on cross-border access to electronic health data and services, including by supporting 'common identification and authentication measures to facilitate transferability of data in cross-border healthcare'.

It is recommended that the "patient identifier" linking unique health records and other clinical documents to individuals is included as an "additional optional attribute" into the structure laid out in the [eIDAS-Attr-Profile]1, in order to enshrine this attribute with the same level of protection as the eIDAS minimum data set, irrespective of national choices for notification of cross-sectorial or health specific eID schemes for the purposes of cross border eHealth.

5.3. NIS Directive

Directive (EU) 2016/1148 of the European Parliament and of the Council of 6 July 2016 concerning measures for a high common level of security of network and information systems across the union (NIS Directive). The objective of the Directive is to achieve a high common level of security of network and information systems within the EU, by means of improved cybersecurity capabilities at national level, increased EU-level cooperation and risk management and incident reporting obligations for operators of essential services and digital service providers.

By imposing a certain number of obligations across the EU, the Directive will help ensure a consistent approach to cybersecurity 'with a view to achieving a high common level of security of networks and information systems within the Union so as to improve the functioning of the internal market'. The main points of the NIS Directive can be summarised as follows:

- **Governance**: Member States must develop a NIS Strategy and designate the appropriate competent authority(ies) to deal with the NIS matters at national level
- **Mandatory information sharing/exchange**: Member States are required to exchange information on good practices and incidents via the CSIRTs network and the co-operation network (both defined in the NIS Directive)
- **Reporting of incidents of significant impact**: operators of essential services (e.g. health, energy, transport, etc.) are required to report incidents of significant impact at their national NIS competent authority.

More specifically Member States are required to:

- Produce and maintain a National NIS Strategy.
- Designate one or more national competent authorities on security and one or more Computer Security Incident Response Teams (CSIRTs)
- Assign representatives to contribute to the 'cooperation network' that will be established to support and facilitate strategic cooperation among Member States.
- Ensure that representatives of the MS' CSIRTs participate in the 'CSIRTs network'
- Ensure that operators of essential services take appropriate and proportionate technical and organisational measures to manage the risks posed to the security of networks and information systems which they use in their operations.
- Ensure that the competent authorities have the necessary powers and means to assess the compliance of operators of essential services with their obligations.
- Ensure that digital service providers identify and take appropriate and proportionate technical and organisational measures to manage the risks posed to the security of networks and information systems which they use in the context of offering services.
- Ensure that the competent authorities take action, if necessary, through ex post supervisory activities, when provided with evidence that a digital service provider does not meet the requirements laid down by the Directive.
- Encourage the use of European or internationally accepted standards and/or specifications relevant to security of networks and information systems.
- Lay down the rules on penalties applicable to infringements of the national provisions to this Directive and take all measures necessary to ensure that they are implemented.

The NIS Directive highlights the importance of establishing a body of common standards and conformity assessment frameworks in order to achieve a consistent level of information security in Europe. Standards and their conformity assessment are referred throughout the Directive.

Article 15a of the NIS Directive, on security requirements and incident notification, establishes that compliance with international standards shall be taken into account in order to ensure a level of security of network and information systems appropriate to the risk presented.

Article 16 of the NIS Directive encourages the use of European or internationally accepted standards and/or specifications relevant to security of networks and information systems.

NIS D came into force in August 2016 and has to be transposed into national law by 9 May 2018, provides legal measures to boost the overall level of cybersecurity in the EU. It aims to achieve a high common level of security through improved cybersecurity at national level (< adoption of national strategies, designation of national competent authorities/single points of contact), increased EU-level cooperation (< creation of cooperation group/Computer Security Incident Response Teams Network) and obligatory risk management and incident

reporting (< establishment of relevant requirements) for operators of essential services and digital service providers. Healthcare providers fall within the scope of the NIS Directive as Operators of Essential Services.

5.4. Refined Health European Interoperability Framework (ReIF)

The Refined Health European Interoperability Framework (ReIF) is a framework for managing interoperability and standardisation challenges in the eHealth domain in Europe. It offers a set of terms and methodologies for reaching a common language, for the analysis of problems and the description of eHealth solutions throughout Europe and is a valuable tool in the decision-making processes related to eHealth projects and solutions. It consists of three parts:

- a refined model for interoperability: a tool to help identify the effort required on 6 distinct operational levels, and the actors and activities involved on each level;
- a template for the uniform description of high-level use cases and for their accompanying realisation scenarios;
- a glossary of terms and definitions, for unifying 'language' and improving understandability

Thus far, the ReIF has essentially been applied in the context of delivery of healthcare. Applied to Patient Registries, it should be adapted on the process layer, to include the function of data analysis/use. The recommendations deriving from the ReIF with regard to updating the PR GL would be to structure the guidelines and recommendations according to the ReIF layer principle or pay attention to cross-layer issues in the recommendations.

6. Emerging Findings

6.1. Progress on Previous Recommendations

The table below summarises the current position in relation to each of the recommendations accepted by the eHN in 2015.

Member States and the Commission agreed to:	
• to promote the inclusion of further registries in the RoR	There are currently over 200 entries on the registry
• to support the dissemination and uptake of PARENT Guidelines	Progressed through HTA and EMA
• to encourage collaboration between the registries and other stakeholders	RD Action has led joint working
The European Commission agreed	
• to explore mechanisms for regular updating of the Guidelines	Addressed through this JAseHN Task 5.3.3

• to integrate PARENT JA deliverables with the work of the JRC	Being developed, in collaboration with DG for Health and Food Safety
• to bring together the experiences of the registries already set up at EU level	As seen in this document, this is beginning to happen
• to pilot the PARENT deliverables on some test cases	Already underway with EUnetHTA
• to explore the usefulness of specific body on health data interoperability	Being assessed in JAseHN WP5
Registry holders and Member States were encouraged:	
• to improve registry quality and interoperability by following and implementing the PARENT Guidelines	The guidelines have been the primary source for the PLEG tool
• to demonstrate the importance of registry data for evidence-based policy making	National e.g. NICE examples
• to increase patients' awareness	This has started to happen for ERNs
• to share the national legislations, plans and strategies	The results from JAseHN Task 6.1.3 will gather some of this data

Table 2-Progress update on 2015 Recommendations

This update is despite there being no project organisation or resources dedicated to following up and maintaining the momentum achieved during the JA's lifetime. Equally, it has been unclear who are the responsible bodies in the MS who would pursue and follow up achievement of the objectives laid out in the Recommendations.

6.2. Findings

Sections 3 and 4 have provided a rich illustration of the many and varied developments in the field of patient registries over the past 2 1/2 years. The work with the HTA centres, especially around the development of the PLEG tool has been a direct application of the outputs from the PARENT Joint Action, and the further development with the EMA initiative has demonstrated the application in support of the assessment and authorisation activities. Alongside this we have seen development of many other registries such as those for cardiology and have seen good use of the PARENT Registry of Registries.

Section 4 describes the many activities in the field of rare diseases with the establishment of the ERNs and the supporting initiatives such as the CPMS to underpin these networks. The RD Joint Action has been bringing together some of the relevant parties and it is clear that there is huge potential for further joint working. At the same time, the different areas of activity illustrate the breadth of use cases being supported and it is important therefore to be careful that we do not seek any „one size fits all" approach. We need to support diversity where appropriate and agree common activities only where benefits accrue.

Deliverable 6.1.3 has summarised the responses from around half of the Member States and identified areas where good progress has been made.

6.3. Issues

As each of the parties have discovered, there are similar issues to be addressed if objectives are to be met, some long standing:

- Sustainability: many current initiatives are supported by short-term or ring-fenced funding and do not yet have agreement on long-term governance or support arrangements
- Interoperability: there is a need for further activity to enable the linkage and exchange of data between registries, and the population of registries from electronic health record data. For instance, it had been noted that interoperability was not identified in the call for tender for ERN whereas it is now clear that this is an important requirement
- Data quality: whilst the PLEG tool provides a rich basis for validation of HTA activities, the more general issues of data quality such as coverage compatibility and consistency need to be worked out further
- Compliance with national and international rules on data protection, security and privacy. The requirements arising from general data protection regulation, eIDAS and the NIS Directive needs to be assessed and addressed. The questionnaire responses to D6.1.3 indicated that for many MS there are no policy arrangements in place to support cross-border linkage of registry data.

There are shared challenges around each of the following

- How to ensure the approach to secondary uses is part of the health policy
- How to incorporate patient reported outcome measures into patient registries
- How best to achieve and maintain stakeholder engagement
- How to operate within the data protection and privacy framework.

7. New opportunities

7.1. Conclusions

The previous section has identified both areas of progress and shared issues. It is important to ensure that good work can continue. At the same time, it is clear that the coherent programme seen in the Cross-border Directive has not been achieved and there is a need to co-ordinate and align activities in order to realise the benefits. Some of the opportunities for joint working include:

- Ensuring those involved in disease registries are informed of their responsibilities under the GDPR, eIDAS and NIS D
- Addressing the fragmentation of data regarding rare disease patients with current activity underway between JRC, the development of a European platform career diseases registration and other cross-border services
- Building on the set of common data elements for rare diseases registration released by the EU RD Platform, to improve the interoperability of patient registries
- Pooling data to combat rare diseases

- JRC and SANTE are developing a European Platform on Rare Diseases Registration (EU RD Platform) to address the fragmentation of data regarding rare disease patients
- The "Set of Common Data Elements for Rare Diseases Registration" is the first practical instrument released by the EU RD Platform aiming for an increased interoperability.

From D6.1.3, it appears that a number of Member States need to co-ordinate ehealth and patient registry activities at national level. Across Europe, the multi-annual workplan for the eHealth Network for 2018-2020, and the proposals for the new Joint Action are based on four areas of action, as shown in the table below. These areas of activity and the task grouping in the new Joint Action offer a good fit to the necessary actions.

Interoperability & standardisation	**Exchange of knowledge**
Monitoring & assessment of implementation	**Global cooperation & positioning**

Table 3-Core topics of Multi-Annual Work Programme

7.2. Recommendations

At the workshop it was agreed that rather than attempting to rewrite the previous guidelines, the focus should be on the future. At the same time, it was noted that recommendations should be set in a context where there is a clear understanding of the stakeholders who need to be engaged, outlining respective roles and responsibilities.

On this basis, recommendations have been identified for Member States and for the eHealth Network (the former one representing the „operational/executive", the latter the political body), on the grounds that these are permanent, and can allocate specific delivery responsibility as appropriate.

The recommendations for Member States focus on aligning national activities and are as follows:

1. to continue to populate and maintain the registry of registries (assuming this is feasible)
2. to designate an NCP for Patient Registries in line with article 6 of the cross-border directive; at Member State discretion, this may be an existing National Contact Point or a separate organisation nominated for this purpose

3. to accredit patient registries to facilitate data exchange with other appropriate registries
4. to inform patients of the importance of registries
5. to support the automatic feeding and linkage of data from other data sources
6. to make patient registries digital and make them part of wider digital infrastructure
7. to enable future extension: data retrieval through distributed query mechanism (eHealth National Contact Points)

The recommendations for the eHealth Network focus on co-ordination of activities relating to eHealth as applied to cross-border care and patient registries in support of HTA authorisation, rare diseases and other relevant activities:

8. to improve communication and co-operation across eHealth activity
9. to identify and define concrete use cases for patient registries.
10. to explore synergies across different initiatives and reduce duplication of effort
11. to engage stakeholders in joined-up action
12. to support joint working with ERNs and other groups
13. to progress the proposed semantic developments for rare diseases
14. to consider the provision of data retrieval through a distributed query mechanism across participating registries
15. to review patient registries according to the ReIF model.