PARENT – Cross-border Patient Registries iNiTiative Joint Action

Patient Registries as support mechanism of Cross-border Healthcare Directive implementation and Future Policy Actions

WP6 Final Report D8

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<table>
<thead>
<tr>
<th>Authoring Team</th>
<th>Persephone Doupi</th>
<th>Arto Vuori</th>
<th>Antti Tuomi-Nikula</th>
<th>Katriina Peltonen</th>
<th>WP1, WP4 &amp; WP5 Leaders (contributors for the Scenarios conceptualization)</th>
</tr>
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<td>NIJZ, HZJZ</td>
</tr>
</tbody>
</table>

Authoring Team:

Persephone Doupi: THL
Arto Vuori: THL
Antti Tuomi-Nikula: THL
Katriina Peltonen: THL
WP1, WP4 & WP5 Leaders (contributors for the Scenarios conceptualization): NIJZ, HZJZ
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Abbreviations

ADR  Adverse Drug Reaction
AHRQ  Agency for Healthcare Research and Quality
AIM  Association Internationale de la Mutualité
APG  Associated Project Group
CEGRD  Commission Expert Group on Rare Diseases
CHF  Chronic Heart Failure
DG MARKT  Internal Market and Services Directorate General
DG SANTÉ  Directive General for Health and Food Safety
(former DG SANCO Directive General for Health and Consumers)
EAACI  European Academy of Allergiology and Clinical Immunology
EAR  European Arthroplasty Registry
ECIS  European Committee for Interoperable Systems
eHGI  eHealth Governance Initiative
EHR  Electronic Health Record
EHR4CR  Electronic Health Records for Clinical Research
EMA  European Medicines Agency
EPAAC  European Partnership for Action Against Cancer.
EPIRARE  European Platform for Rare Diseases Registries
epSOS  European Patients – Smart Open Services
ERA  European Research Area
ERN  European Reference Networks
ESC  European Society for Cardiology
ESIP  European Social Insurance Platform
EUBIROD  EUniverse BBest Information through Regional Outcomes in Diabetes
EUCERD  European Union Committee of Experts on Rare Diseases
EuraHS  European Registry of Abdominal Wall Hernias
EureMS  European Register for Multiple Sclerosis
EUnetHTA  European Network for Health Technology Assessment
EUROCISS  European Cardiovascular Indicators Surveillance Set
EUROCOUSE  Europe against Cancer: Optimisation of the Use of Registries for Scientific Excellence in research
HHS  Department of Health and Human Services (US)
HTA  Health Technology Assessment
IMI  Innovative Medicines Initiative
IMIA  International Medical Informatics Association
JAsEHN  Joint Action in support of the eHealth Network
JRC  Joint Research Center
MAH  Marketing Authorization Holder
NORIA  Nordic Research and Innovation Area
OMP  Orphan Medicinal Product
PAES  Post Authorization Efficacy Studies
PASS  Post Authorization Safety Study
PARENT  Cross-border PAatient REgistries iNiTiative
PHR  Personal Health Records
PMCF  Post Market Clinical Follow-Up
RD-ACTION  Rare Diseases Joint Action
Executive Summary

PARENT Joint Action brought EU patient registries into the spotlight, by examining their role and possible utilization in the context of implementing Directive 2011/24/EU, the Cross-border healthcare directive. PARENT acknowledged that research performed with the aid of patient registry data can provide answers to issues critical in the assessment of effectiveness and efficiency of healthcare services, which in turn are essential to the quality and sustainability of healthcare systems as a whole.

Work Package 6 of the PARENT Joint Action has had a two-fold objective:

- Provide a specific plan of activities and policies to further develop eHealth-enabled registries as a support mechanism for the implementation of the Directive on cross-border health care – the focus of the report at hand.
- Explore and address issues related to cross-linking and sharing of registry data. Ensure sustainability of cross-border collaboration on secondary use of registry data, incl. the Registry of Registries, Methodological and Governance Guidelines – the topic of Deliverable D9, Sustainability of cross-border collaboration on secondary use of registry data - Business models Analysis.

In the first stage of our work (presented in the Interim Policy report of June 2013) we produced a preliminary outline of the relevant policy issues to be addressed in the subsequent phases of the Joint Action. We utilized a combination of several data sources, which are outlined in more detail in the respective sections of the report:

- grey and scientific literature (results presented in Sections 3 and Annex 3 respectively),
- current and proposed legal and regulatory framework (overview and results presented in conjunction with specific scenarios such as pharmacovigilance and medical devices surveillance),
- work undertaken and underway by EU-funded projects in the area of registries, as well as EHRs-eHealth, as represented in the PARENT Associated Projects Group (APG).

In subsequent stages, and in addition to updating as necessary parts of our earlier work we delved further in identifying potential roles for patient registries in conjunction to the Directive’s various requirements (see Annexes 4 and 5 for details) and engaged in an iterative process of drafting policy proposals and adapting them according to APG members’ and stakeholders’ feedback. The Directive analysis had already brought forward the main areas of relevance, confirmed also through our other streams of work: European Reference Networks, Rare Diseases, HTA (in first instance of pharmaceuticals and medical devices).

With regard to the legal and regulatory landscape, the overarching issue has been the forthcoming Data Protection Regulation and its impact on the operational framework for secondary use of health data. After a lengthy period of uncertainty and ambivalence for the research community, the process is drawing to a close, with the successful conclusion of the triilogue negotiations in December 2015. It appears that the so called “legitimate interests” (other than consent) for using health data for patient registries purposes will continue to exist. As a result, Member States will be able, as they are today, to provide exceptions to the requirement of consent, setting up patient registries on different legal bases such as national laws and/or permissions from competent authorities.

The amendments in the legislative framework concerning both medicinal products and medical devices – although at a difference stage of progress – have a clear emphasis on ensuring patient and consumer safety. In the case of medicinal products, the new legislation imparts the recognition of post-authorization safety and efficacy studies (PASS, PAES), while the reform of the Medical Devices Directive aims at promoting better traceability of devices throughout the supply chain. In both cases, there are growing
expectations for increased utilization of post-marketing, real world data, thus making registries and their suitability for the task a case in point.

The secondary use of health data is a complex and multidimensional issue, which has been the subject of analysis and various proposals by many groups, institutions and individuals already for decades. In this continuous debate, patient registries – although a well-established source of health data – have not figured very prominently. Infrastructures and solutions for remote use of health (and other) data are an area where significant work is already in progress (such as, e.g. the Data without Boundaries project). The outcome of these efforts will play a central role in defining the landscape in which also the solutions for cross-border use of registry data will come to operate. In this respect, the mapping of the situation in EU MS regarding strategies for the utilization of health data resources has provided some useful insight as to the baseline situation. How each country has decided or plans to address this topic is a policy issue and a political decision of strategic significance. Alignment of activities and approaches cannot be taken for granted, even in cases of countries were long traditions of collaboration exist, such as the experience of the Nordic countries has indicated. And yet, coordination and avoidance of developing non-interoperable solutions are of the essence.

PARENT has brought forward three pairs of policy objectives (inspired by the values and principles underlying Directive as well as the objectives set by the 3rd Health Programme Regulation) and respective policy actions:

1. Creating a digital infrastructure supporting public health & medical research - **Action: Placing interoperable patient registries’ on the eHealth agenda**
2. Access to better and safer healthcare for Union citizens - **Action: Promote patient registries’ as tools for ERNs and rare disease services & research**
3. Contribute to innovative, efficient and sustainable health systems - **Strengthen use, usefulness and suitability of registries for HTA-based patient and consumer safety and monitoring**

In addition to these objective-action pairs, we have proposed for consideration by the Member States and the EU scientific and expert community in eHealth and related disciplines the concept of a National Contact Point for Registries (R-NCP). The idea was born out of two distinct needs: on the one hand, to ensure dissemination, uptake and consistent use of PARENT deliverables and tools on Member State level and on the other hand the prospect of bringing PARENT Framework services forward in the future, towards brokering services for health data (see Report D9 for more details).

The period of activities of PARENT Joint Action coincided with a particularly active, dynamic and productive period in the EU digital health landscape. Many steps forward have been taken towards creating the prerequisites for interoperable cross-border eHealth services, addressing all layers of the European Interoperability Framework. PARENT JA has succeeded in bringing EU patient registries in the spotlight as valuable health data resources, worthwhile to be seen and understood as an indispensable part of the Digital Europe infrastructure. We have developed a clear added value proposal, the necessary tools for its implementation and a proof-of-concept version of the operational mode of the Framework. In addition to developing together with our collaborating projects and stakeholders a set of proposals for policy actions, we have been fortunate to even see some of them already changing into concrete action steps, such as in the area of Rare Diseases and European Reference Networks (see Annex 2).

PARENT JA deliverables will be tested and assessed through various projects and initiatives in the next two to three years including:

- the forthcoming EU platform for Rare Disease of the EC Joint Research Center
- the pilots of the soon starting EUnetHTA JA3, as well as EMA pilots
- the assessment of PARENT Guidelines through JAseHN JA activities
- Possible R&D projects under the IMI and Horizon 2020 funding programmes.
Experiences and feedback will be accumulated through these hands-on experiences and depending on the outcomes policy and action priorities will need to be revisited, along the rest of PARENT deliverables. The opportunities for linking the work in patient registries with the activities ongoing in the areas of biobanking and research infrastructures, as well as the new prospects opening through linking citizen and patient-collected data to patient registries are some of the prospects already visible in the horizon.
1  Current Challenges and Opportunities for EU Patient Registries

1.1  The value of Health Data

_Societies without good data risk poor health care quality and lost innovation._

The statement from the 2015 OECD report Health Data Governance Privacy, Monitoring and Research (1) summarizes succinctly the drive behind the work of PARENT Joint Action. Data – and health data as a most valuable sub-set– has become an asset for EU economies and societies, alongside human and financial resources. Patient registries, often long-standing, curated collections of health data in many EU Member States are presently an under-utilized resource. At the same time, other MS are just beginning to develop their registry infrastructure. Registries present differences in content (clinical, population-based etc.), semantics (meaning), quality, update frequency and completeness. It is precisely these differences that pose a significant limitation to the ability of using data across registries within a country, as well as – and even more so-- across countries. At the same time the need to share and combine registry data (individual or anonymized and aggregated) is increasing as a result of the growing emphasis on comparative research. Clinical effectiveness, efficacy, cost effectiveness, quality of treatment and vigilance are themes that span organizations, clinical fields and geographical borders. Moreover, the parallel growth and developments in the area of eHealth most often progress in a separate path from the activities of patient registries. The result is a lost opportunity in gaining the most out of the investment, development and roll out of the regional, national and EU eHealth infrastructures.

1.2  The role of the PARENT Joint Action and Framework

Against this backdrop, PARENT (Cross-border Patient Registries Initiative) Joint Action begun its journey, aimed at addressing the problem of lacking interoperability between registries and inadequate utilization of the increasingly modern eHealth infrastructure in the creation, maintenance and development of patient registries. PARENT’s main targets were as follows:

- **Aim:** to rationalise and harmonise the development and governance of patient registries, thus enabling analyses of secondary data for public health and research purposes.
- **Goal:** support MS in developing comparable and coherent patient registries in fields where this need has been identified (e.g. chronic diseases, rare diseases, medical technology)
- **Goal:** support MS states in the provision of objective, reliable, timely, transparent, comparable and transferable information on the relative efficacy and effectiveness of health technologies.

The PARENT Framework is the means of making available different but connected PARENT deliverables (guidelines, best practices, data models, software components etc.) in a meaningful and comprehensive way. The purpose of the Framework is to provide Member States, patient registry holders and registry data users with the policies, guidelines, and tools necessary to support interoperable patient registries and exchange of data between them. More specifically, the modules of the Framework are the following:

1.2.1 Registry of Registries (RoR) [http://www.parent-ror.eu](http://www.parent-ror.eu)

One of the key PARENT framework key components is the Registry of Registries (RoR).

The objectives of the PARENT Registry of Registries on the onset of the JA had been described as follows:

- PROVIDE a pilot listing of available registries on EU level
- SHARE comprehensive information on which data are collected/available in a given registry
- SET-UP a web platform allowing direct queries for specific data on a given registry.
In its first stage of development, the RoR was a searchable web catalogue of Member States and EU-level patient registries’ descriptive data obtained through the PARENT Questionnaire to registry holders. In its second phase of development the RoR v. 2 incorporates the PARENT Assessment Tool. The Tool enables registry self-assessment for MS registries and institutions on the basis of data quality and interoperability readiness criteria, which were recognized as most worthy for assessing according to the feedback received at the 5th workshop of WP4. The Assessment Tool criteria have been mapped to the content of the PARENT Guidelines.

### 1.2.2 Guidelines and tools for registry creation, maintenance and update

The PARENT Methodological guidelines and recommendations for efficient and rational governance of patient registries (the Guidelines), published in October 2015 provide practical and ‘hands on’ advice for setting up and managing patient registries, enabling secondary use of data for public health policy and research and preparing for cross-border operations. The Guidelines, available in both paper and Wiki format (parent-wiki.nijz.si/), are accompanied by further assistive tools, such as data models and the Assessment Tool.

**EU POLICY LANDSCAPE: Legal Framework**

- Directive 2011/24/EU
- Regulation on 3rd Health Programme
- Data Protection Regulation
- Pharmacovigilance Directive
- Medical devices Directive
- ERN Delegated & Implementation Acts
- Council recommendation on RD
- Clinical Trials Directive
- Public health statistics Decree
- Council Recommendation on cancer screening

![Figure 1. Overview of key legal & regulatory framework for PARENT policy analysis](image)

### 1.2.3 Sustainability and future policy actions

Work Package 6 of the PARENT Joint Action had a two-fold objective:

- Provide specific **plan of activities and policies** to further develop eHealth-enabled registries as a support mechanism for the implementation of the Directive on cross-border health care (the focus of this Report – PARENT Deliverable D8).

- Explore and address issues related to cross-linking and sharing of registry data. **Ensure sustainability of cross-border collaboration** on secondary use of registry data, incl. the Registry of Registries, Methodological and Governance Guidelines (see PARENT JA deliverable D9: Sustainability of cross-border collaboration on secondary use of registry data - Business models Analysis, for the respective results)

In order to effectively approach our first task we utilized a combination of several data sources, which are outlined in more detail in the upcoming sections of the report:
- the scientific and grey literature (through the literature review),
- the current and proposed legal and regulatory framework, (see Fig. 1)
- the activities of international organizations and initiatives
- the views of public and industry stakeholders.
- the work undertaken by EU-funded projects in the area of registries, as well as EHRs-eHealth, as represented in the PARENT Associated Projects Group (APG).

![Central instrument in collaboration activities](image)

Figure 2 PARENT JA Associated Project Groups instrument

The Associated Projects Group was a collaborating body established by PARENT Joint Action with the purpose of ensuring communication and wherever possible collaboration between the JA and projects related to either registries or eHealth development (see Figure 2). The APG has served the PARENT work in multiple ways: a central instrument in our collaborative activities the APG has brought together projects and actors in the field of patient registries (many of them from the Rare Diseases community, but also from fields such as diabetes and cancer) as well as representatives from the field of eHealth and public health policy and research.

Associated Projects Group members provided direct feedback to PARENT deliverables already at the point of their production, through:
- active participation in PARENT events and workshops
- sharing and review of materials addressing common or related topics
- providing ideas and experiences in meeting specific challenges, particularly in the areas of interoperability and sustainability.
- being collaborators towards achieving shared and commonly identified goals.

The primary focus of the work undertaken at the start of PARENT by WP6 focused on identifying potential roles for patient registries in conjunction to the Directive’s various requirements and producing a preliminary outline of the relevant policy issues to be addressed in the subsequent phases of the Joint Action.
2 Analysing Directive 2011/24/EU: medical information needs and the role of patient registries

The Directive on the application of patients’ rights in cross-border healthcare (2) or, as often called for short, Cross-border Healthcare Directive was adopted by the European Council in February 2011, following a long period of negotiations and preparatory actions. Member States were expected to have made the necessary adaptations to their national legislation by October 25, 2013 (Fig 3).

The legislative process

Adoption of the Commission proposal: 2 July 2008
First reading: July 2008 - September 2010
Second reading:
Sept. – Dec. 2010: Negotiations
19 January 2011: Vote in Parliament
28 February 2011: Formal adoption of the Council
4 April 2011: Publication in the Official Journal
24 April 2011: Entry into force
Transposition time: 30 months (25 October 2013)
The Committee on Cross-border Healthcare: 21 June 2011

The Committee on Cross-border Healthcare: 21 June 2011

Figure 3. Legislative process timeline of Directive2011/24/EU (from Nowak, 2011)

The Directive has the main aim of providing a clear legislative framework that enables EU-MS citizens to freely seek and receive care from anywhere within the EU. The cooperation between health systems envisioned by the Directive is focused on four major areas:

a. Recognition of prescriptions;
b. European Reference Networks;
c. Health Technology Assessment and
d. eHealth – the latter for the purposes of safety and quality of care, continuity of care, and health research.

It is within the context of the eHealth-focused activities that PARENT Joint Action took place. More specifically, Article 14b) ii. of the Directive defines that the Union shall (through the actions of the established eHealth Network):

“...draw up guidelines on... effective methods for enabling the use of medical information for public health and research”. The objective shall be pursued in due observance of the principles of data protection as set out, in particular, in Directives 95/46/EC and 2002/58/EC.

In order to acquire a wider perspective in our policy analysis and address the WP6 task of defining how patient registries can be utilized in support of the Cross-border Healthcare Directive implementation, we have proceeded by approaching the Directive as a whole and from a more generic perspective. Namely, we set out to identify what are the possible medical information needs generated directly or indirectly by the Directive’s various requirements, whereby ’medical information’ can be understood potentially, but not exclusively in the form of patient registry data. We aimed to get a more comprehensive picture as to the
possible ways registries can be utilized in support of the Directive’s implementation, and to trace the prerequisites for such options to be realized.

2.1 Method of work

The full text of the Directive was reviewed by two WP6 team members independently to identify sections relating either explicitly or indirectly to registry data use in specific, or medical information use generally. We entered the respective extracts of the Directive to an Excel spreadsheet, accompanied by the reference to the corresponding Article or Recital number. We also documented the reasoning of our selections, from the point of view of the activities and objectives of PARENT Joint Action.

Once we identified cases of medical information needs, we proceeded to produce a list of the stakeholder groups potentially involved and/or affected in each case. We documented the roles and tasks attributed to them by the Directive and also provisionally outlined the respective roles and interests of other stakeholder groups not explicitly mentioned in the text.

After the first phase of data extraction was completed, we compared our results and arrived at consensus by discussing areas of different interpretation. The results we present here are more heavily based on the analysis of Directive Articles, rather than Recitals regarding the overarching principles underpinning the Directive, the possible use cases for patient registries, as well as certain themes emerging from the analysis of the Directive text, which we found to be of relevance for the work of PARENT Joint Action. Although we have grouped findings under certain prevailing headings, there are natural overlaps and connections between these areas, which we have tried to make explicit in the text.

2.2 Values and principles underlying EU cross-border collaboration in health

At the time that healthcare services were excluded from the scope of the Directive on services in the Internal market, the 25 (at the time) Health Ministers of the EU produced a statement on the common values and principles underpinning Europe’s health systems, endorsed by the Council in its Conclusions of 1-2 June 2006 (Council Conclusions on Common values and principles in European Union Health Systems, 2006/C 146/01) (4). Those same values and principles are also reflected in the Cross-border Healthcare Directive and provide the basis on which several actions have been proposed and bodies established.

The overarching values guiding the provision of healthcare services are those of Universality, Access to good quality care, Equity and Solidarity and are referenced in Article 4.1. of the Directive. The values are subsequently translated into a set of operating principles that are “shared across the European Union”. Here we find:

Quality, Safety, Care based on evidence and ethics, Patient Involvement, Redress, Privacy and Confidentiality. These principles are indeed reflected and covered in specific actions of the Directive, as follows:

Quality and Safety: (Articles 1.1, 4.2b, 12.2c, 12.2g, 12.4.iii, 14.2bi, Recital 29)

Care based on evidence and ethics (Article 15)

Patient involvement and Redress: (Articles 4.2b, 5, 6, Recitals 20, 23, 48, 49)

Privacy and confidentiality: (Articles 2, 4, 5, 10, 11, 14 - Recitals 25, 63).

In addition, the Directive makes reference to the following principles:

---

1 Recitals and Articles: Generally, the initial sections of a written contract will be referred to as the recitals. Descriptive and factual information, such as the identities of the parties, the background, and most importantly, the purposes of the contract are recited there. The recitals can be contrasted with the body of the contract, which contains the obligations to be undertaken. (Klimas T, Vaičiukaitė J. The law of recitals in European Community legislation)

13
• **Free movement of goods, persons (patients) and services** (freedom to provide medical services and to receive services also through eHealth/telemedicine) – (Recitals 11, 21, 26, 29)

• **Objectivity, non-discrimination/equal treatment, transparency** (Recital 47)

• **Data protection** (article 14)

• **Good governance** (Article 15, HTA network)

• **Recognition of prescriptions and medical devices** (Article 11, Recital 53)

• **Subsidiarity and proportionality** (Recital 64)

Taking stock of the values and principles serving as the basis for the Directive is essential in understanding both the framework in which PARENT Joint Action has operated, as well as the grounds for the division between Member States’ and EU-institutions’ competencies and areas of action.

### 2.3 Roles for patient registries as emerging from Directive 2011/24/EU

#### 2.3.1 Key areas: ERNs, Rare Diseases, HTA

Given our starting point – which was to identify the role of registries in support of the Cross-border Healthcare Directive through analyzing its content – a central and partly unexpected finding was the fact that registries are explicitly mentioned in the Directive just one single time – in the context of European Reference Networks, one of the main areas of collaboration between healthcare systems. The relevant aspects of the respective article (Art. 12) are presented in more detail in Annex 4, Table 1. Since the Directive indicates as one of the most suitable areas for ERNs that of rare diseases, it can be assumed that **rare disease registries** should also be an area of focus. Although in the respective article (Art. 13) there is no reference to registries, the topic is explicitly addressed in the Communication on rare diseases (COM(2008) 679 final). Moreover, through PARENT work with APG members we were aware of the rich activity and important developments evolving in the area of rare diseases. With additional confirmation on the high policy relevance of this work, we pursued the further enhancement of communication and collaboration between PARENT and parties active in the field of rare disease registries. The very fruitful outcome of this collaboration is reported later on in this report (See Chapter 6 and Annex ).

In addition to this direct reference to registries, we have identified several other potential uses of patient registries – such where registries are not directly mentioned in the Directive text as the source of data or information, but can be reasonably assumed as (at least one) implementation alternative. The strongest of these cases is the one of **Health Technology Assessment**, in the context of studying relative efficacy as well as the short- and long-term effectiveness, when applicable, of health technologies. In that context, registries could function as the source of real-world data. Indeed, our close collaboration with HTA colleagues during the second half of PARENT provided confirmation of this finding and indicated several areas where further work could be focused.

Other potential uses of patient registries are in:

- **Support of patients’ informed choice**, as indicated in Article 4 (under healthcare providers’ responsibility);

- Determining the upholding of **non-discrimination in fees for care**;

- Preparation of **reports on the operation of the Directive** as indicated in Article 20. Of the articles relating to Implementation & final provisions (Chapter 5, Articles 16 – 20) direct relevance for registries lies perhaps in Article 20, specifying that as of “…25 October 2015 and subsequently every
3 years thereafter, (the Commission) will draw up a report on the operation of this Directive and submit it to the European Parliament and to the Council”. Perhaps that is another role for registries in the form of important data repositories to feed the needed analysis.

It is important to note that in the aforementioned use cases the focus is on follow up and monitoring of services through patient registries which also often means healthcare providers’ registries or databases (instead of e.g. national or regional ones). A project exploring a relevant scenario in this area was HonCab (www.honcab.eu) which supported the creation of a pilot network of hospitals related to payment of care for cross border patients.

### 2.4 Important points for the work of PARENT Joint Action

In addition to identifying use cases for patient registries as emerging from analysis of the text, there are a number of other important points and elements brought forward in the Directive, which PARENT should take into account in any further work and respective proposals to be developed.

- **Article 3** contains an abundance of definitions relevant for PARENT, such as healthcare, insured person, MS of affiliation, MS of treatment, cross-border healthcare, health professional, healthcare provider, patient, medicinal product, medical device, prescription, health technology, medical records. Of particular relevance: health technology, medicinal products, medical devices, medical records.

- **Article 7** deals with the reimbursement framework for cross-border services and could be indirectly relevant for PARENT, if registries would be part of some follow up/monitoring mechanism, as mentioned earlier regarding the example of HonCab.

- **Article 8** defines healthcare subject to prior authorization, and with the exception of some references to issues of safety and quality there is no direct relevance for PARENT. **Articles 9 and 10** cover respectively administrative procedures, as well as mutual assistance and cooperation and are not of direct relevance either, except (perhaps) the mention on use of ICT in healthcare provision.

- **Article 15** on Health Technology Assessment also covers the principle and operationalization of good governance, which is relevant as reference model for the development of sustainable business solutions for PARENT. In the same article, the possibility of seeking further joined funding as part of methodological work is being raised.

- The topic of interoperability and its various aspects is addressed by several articles (see Annex 2, Table 1) and points PARENT to the elements that should be taken into account when developing its own guidelines and proposed technical solutions.

- **National competencies vs. areas where EC/EU level action is needed**

Healthcare has traditionally been one of the policy areas where the division of competencies between EU institutions and Member States’ policy making actors is a sensitive albeit constantly negotiable topic. This balancing exercise is reflected in several areas of the Cross-border Directive as well (see Annex 2, Table 2 for a list of areas and the respective Articles where they are referenced). Often it is the case that the need for policy level action on the EU level is recognized due, for example, to the complexity of the matter at hand. Any implementation actions, however, are largely dependent on the willingness and ability to progress on the national level.

In PARENT, this tension is reflected in the area of adoption of eHealth solutions in the provision of healthcare services. The status of progress is still variable across Member States, but any possibility
to truly advance towards interoperable, IT-enabled registries relies on the implementation of a national infrastructure featuring the elements necessary for eRegistries to operate.

### 2.5 Progress of Directive implementation

The Commission released an evaluative study on the cross-border healthcare Directive (2011/24/EU) on May 28 2015 (5). In September the same year, the Commission delivered its own report on the operation of the Directive to both the European Council and European Parliament (6), thus fulfilling the requirements of Art. 20 of the Directive. The latter report, which made use of the findings and materials of the evaluative study, came two years after the deadline for transposition of the Directive 2011/24/EU on the application of patients’ rights in cross-border healthcare into Member States’ legislation (25 October 2013). The overall results paint the picture of a process in its very early stages and in a sense form the baseline for future more in depth comparisons and analysis:

1. a number of Member States were late implementing the Directive,
2. the number of citizens who are aware of their general rights to reimbursement were extremely low. And even where citizens were aware of their rights, there were a number of Member States where it is difficult for patients to find out more about how to exercise them in practice. In that regard, the performance of National Contact Points presented considerable variation.
3. While some Member States had implemented the Directive fully and were making considerable efforts to facilitate patients’ rights to cross-border healthcare, there was also a considerable number of Member States where the obstacles placed in the way of patients by health systems were significant, and which, in some cases at least, appeared to be the result of intentional political choices.
4. Natural demand for cross-border healthcare may be relatively low for a number of reasons: unwillingness of patients to travel (e.g. because of proximity to family or familiarity with home system); language barriers; price differentials between Member States; acceptable waiting times for treatment in the Member State of affiliation. It is also worth noting that some of the demand that does exist may be catered for under local bilateral arrangements, which exist in some Member States.

At the same time, the Commission’s operation report contains some points of high relevance for PARENT:

- First the observation that “the impact of the Directive should be considered more widely than simply cross-border healthcare. It has contributed to a number of important discussions going on in many Member States regarding healthcare reform… leading to “…transparency for patients on their rights, and on the quality and safety of healthcare services”.

- Through the chapter of the Directive on cooperation between health systems a new framework for Member States’ cooperation has been created. This is deemed as a development able to deliver concrete benefits to health systems across the EU. The European Reference Networks are raised as an example which could seriously improve access to care for rare / low-prevalence and complex diseases where expertise is rare. To realise this potential, ongoing support and commitment from all sides will be needed.

- Last but not least, the report concludes with regard to cross-border collaboration with the same observation that PARENT has found as decisive for the success of its work: Successful cross-border collaboration requires significant buy-in from local-level actors, with the support of national authorities.
3 Secondary use of health data: mapping stakeholders’ views

The utilization of patient registries’ data is essentially part of the broader theme of secondary use of (health) data (7) – either secondary use of the data stored in the registries themselves or secondary use of the data stored in patients’ health (and social) care records, from which they are channeled to registries. Through review of relevant publications, workshop and seminar reports, project materials, as well as the work undertaken by PARENT partners themselves we have traced the main trends of different stakeholder groups on the subject of secondary use of health data. We present here the key points we have distilled organized along three levels of activity: international, European and Nordic.

3.1 International initiatives

One of the earliest comprehensive studies that we identified on the subject of secondary health data use dates from 2002 and it was produced by the Canadian Institutes for Health Research (8). The report summarizes succinctly the key tensions to be addressed around secondary use of health data in a manner which remains as timely and urgent today as over ten years ago.

The challenge facing us today is to reach a workable and practical balance between the value EU citizens place on the improvement of their health, the effectiveness of their health care services and the sustainability of their health care system, and the equally compelling value they place on their right to privacy and confidentiality with respect to their personal information(2, modified).

In 2008, the World Health Organization and the Wellcome Trust initiated discussions about the development of a common Code of Conduct on the sharing of data of public health importance (9). In 2011, the Wellcome trust and their collaborators established the Public Health Research Data Forum. A group of major international funders of public health research have committed to work together to increase the availability of data emerging from the research they fund, in order to accelerate advances in public health. A joint statement of purpose sets out the principles and goals through which these organisations intend to work towards this shared vision.

The World Economic Forum published in 2010 its report: “A Review of the Health Data Landscape: Trends, Successes and Gaps”. The analysis framework proposed in the report demonstrates that the fundamental health data issue relates to the balance of having access to health data, while protecting an individual’s privacy, and also draws attention to the health data inequities/disparities being experiences around the world.

With regard to the subject of access to data, the following observations are made (direct quotes):

- Creating a fully computerized, all-inclusive, quickly accessible source (i.e., inventory) for health data would add a margin of confidence to the delivery of healthcare. In addition, it would provide a resource for medical researchers tracking the origins of disease and the effectiveness of treatments.

- Knowing what data are out there, where they are, and how to access them would be very valuable. Although some health data organizations have initiated the development of an electronic framework for the creation of an inventory of health data (e.g., a collaborative of Canadian health data organizations), there do not appear to be any comprehensive global inventories of health data sources built to date. The reason for this delay is most likely because there are some critical questions yet to be answered pertaining to a number of pre-requisites to building this type of inventory, such as:
  - Conceptual model design – what is the nature of the inventory, how will it be structured, how will it be utilised, how often will it be updated, etc.?
  - Stewardship – who will assume responsibility for building, populating and maintaining such an inventory?
Funding – from what source(s) will the considerable funding needed for both start-up and ongoing operating costs come?

Alignment – how will these efforts be aligned with other work that is currently underway or being planned on a global level?

With health data increasingly acknowledged as a prerequisite to effective and efficient health management, the World Economic Forum has led the development of a Global Health Data Charter (10). This chart is an expression of the commitment made by a group of organizations to collaborate and work towards addressing key health data gaps. The aim is to develop health data management not through mandating regulations or defining implementation practices, but rather by using the charter as a foundation document that can be leveraged at all levels. It is recognized that there will be different approaches taken by different jurisdictions in their implementation of the Charter, however, the assumption is that all of the components of the Charter need to be addressed in order to ensure success. In February 2013, the World Economic Forum has published yet another report of interest (focusing on the industry view on the subject): Unlocking the Value of Personal Data: From Collection to Usage (11).

The Organisation for Economic Cooperation and Development (OECD) published in 2010 a detailed report on the subject of “Improving Health Sector Efficiency: The Role of Information and Communication Technologies” (12). The report discusses among other things the issue of standardization and interoperability, as well as the necessary privacy and security framework.

In the context of the activity on “Strengthening health information infrastructure for quality measurement: data linkages and use of electronic health records” several activities relevant to the focus of PARENT Joint Action have taken place.

The 2010 Health Ministerial Communiqué noted that health care quality improvement requires more effective use of data that has been already collected, for the purposes of which a Joint consultation with the OECD Working Party on Information Security and Privacy about privacy protection challenges in the use of personal health data was initiated.

A survey of over 20 countries has been performed concerning their current practices and stage of progress on the use of personal health data to monitor health and health care quality. The survey found considerable cross-country variation – linked to differences in risk-management in balance of data access and data privacy. The following sources of variation were identified based on whether or not:

- An exemption to patient consent requirements may be granted;
- Authorities holding data needed for a project (data custodians) will share data with other government authorities;
- It is clear with whom to request approval and what are the criteria to obtain approval;
- There are mechanisms for privacy respectful access to data.

The group has proposed on-going monitoring of the development of personal health data and the use of these data for health and health care quality monitoring and research through a 2013 survey of countries, and a further survey in 2015 on electronic health record systems and the use of these data for health care quality monitoring. Further activities of relevance for PARENT are the proposal to develop:

- An international health data privacy lexicon providing common terms of reference for privacy and health experts;
- A taxonomy of risk in the usage of health data, determining which procedures should be implemented for any specific level of risk
- Promising practices including privacy by design and privacy-enhancing technologies enabling secure access to each category of data.

The report “Health Data Governance: Privacy, Monitoring and Research” (1) published in summer 2015 examined the status of data availability, uses and governance practices and identified key data governance mechanisms that maximise benefits to patients and societies while minimising risks to patients’ privacy and to public trust and confidence in health care providers and governments. Among 22 countries reviewed, all the Nordic countries plus the UK (Wales and Scotland) were found to be in the forefront of development,
presenting mature solutions. The study identified several areas where international collaboration would be needed, including:

- ensuring that there are sufficient agreed international standards for data coding and interoperability;
- support countries to evaluate which national legal frameworks for the protection of health information privacy provide adequate protections to facilitate multi-country statistical and research projects.

On a practical level, the study also provided a risk-benefit evaluation tool which countries could use to guide bodies evaluating and approving applications to process personal health data. The tool addresses both societal benefits and societal risks.

### 3.2 European Initiatives

The Friends of Europe think tank, together with Novartis and Glaxo Smith Klein organized in November 2012 in Brussels a Policy Summit entitled: **Why health is crucial to European recovery**. The Summit focused on health innovations, research and collaboration at European level. The meeting had several speakers from different offices and companies.

From PARENT’s point of view the summit was important for policy and stakeholder issues. The speakers demanded more health data and information to support innovations, research and policy making. Particular concern was expressed with regard to **lack of cost-effectiveness information**. They also thought that there should be more data about importance of prevention. **Registries were mentioned only in connection to rare diseases.** Speakers found rare diseases data sources, including registries, as an excellent example of European level research and collaboration. However, representatives of pharmaceuticals industry also demanded more personal patient data for their own purposes (cost-effectiveness, research, innovations).

As a conclusion the speakers underlined that existing data sources should be utilized more effectively at European-level for research and innovation purposes. **Collaboration between private and public** should be flexible and the importance of collaboration between industry, national institutions, universities and patients should be recognized. Europe has to question practices and re-think how to organize health care. Nevertheless, no concrete ideas and approaches were presented how to utilize existing health data at European level. It seems that the desire to use cross-border data (including registries) efficiently exists, but the data and information of the data itself should be better available. **Tools and practices for policy makers to understand the information was seen essential for improvement** in this matter. The main messages emerging from the summit underlined that PARENT’s contribution could be essential in offering concrete approaches to sharing and utilizing cross-border health data.

**WHO-IMIA Industry Stakeholder Consultation On Health Data Reuse, 27.2.2013, WHO Headquarters, Geneva.**

The event was meant to be a stepping stone for the 2013 European Summit on Trustworthy Reuse of Health Data, held in Brussels 3.-4.6.2013. The objectives of the meeting were to exchange views on the use of (individual) health data obtained from electronic health records, discuss the challenges of data reuse in terms of governance, transparency, and related ethical and commercial concerns. The participants represented health information technology and information technology companies, data aggregators, insurance and pharmaceutical companies as well as universities and the WHO.

The discussion was mainly on a conceptual and ideological level. The most debated topics included EHR’s, clinical trials, business opportunities for health data collectors and users, including possible dividend back to patients, and above all **ethical issues concerning the use and safety of health data**, which centered around the patient and his/her anonymity. The most used word in the meeting was clearly “trust”, on which all efforts and systems on the field should be based. Many interesting ideas were presented, concerning e.g. who should have access to health data and on which conditions, linkage of health data with other personal data, and the role of governments in controlling data reuse. The basis on the discussions was the **commercial use of health data**, without references to scientific research or open data.
2013 Transnational Summit on Trustworthy Use of Data for Health, Brussels 3-4 June 2013.
The event was the second of its kind (the first one, the European Summit on the Trustworthy Reuse of Health Data, had been organised a year earlier, again in Brussels). WHO and IMIA (International Medical Informatics Association) sought to explore how data for health is obtained, curated and shared across borders of every kind in the context of what they called ‘the health data economy’. The change in phrasing from ‘health data’ in 2012 to ‘data for health’ in 2013 was not a trivial one, and it reflected the shift of focus toward a very broad range of data, far beyond that contained in ‘traditional’ patient records and registries. The following were among the main themes of the two-day discussions:

- **Challenges, opportunities and principles in building public trust around use of data for health.** Explored through different angles: industry, government, academia.
- **Big Data.** Primarily the focus of the industrial co-organisers (Oracle, Cisco, Astra Zeneca, Pfizer) who have shifted/widened their focus from traditional electronic patient record data to all sorts of data (PHR – personal health record, ie. data directly entered by the patient, social media data related to health and lifestyle, health and well-being related apps collecting data from individuals ranging from eating and sleeping habits, to emotional state etc.), geographic/location data etc.
- **Trust(worthiness)** and how to achieve it for industry, scientists/researchers and other stakeholders. Key components proposed were: education (of citizens/patients and policy makers), improved communications (particularly in terms of understandability), codes of conduct, transparency, demonstration of benefits, best practices and success stories.
- **Privacy topics:** the role and mode of informed consent, the right to be forgotten, ownership of data and the impact of the forthcoming Data Protection Regulation.
- **Future of Medicine scenarios** – impact and implications, emphasis on biomedical/genomic data. Need for linking with phenotype (ie. classic patient record content)

3.3 Nordic Initiatives

Nordic countries are well known for their registry tradition, as well as their culture of cooperation and collaboration. Hence their experiences form a valuable starting point when approaching the subject of cross-border use of registry data. We provide here a brief overview of main relevant structures and activities around Nordic health registries development and collaboration.

3.3.1 NordForsk

NordForsk is an organization under the Nordic Council of Ministers that has the responsibility of promoting co-operation on research and research training in the Nordic area. NordForsk provides both funding for research cooperation as well as advice and input on Nordic research policy. Policy relevance is one of the strongest criteria for identifying concrete research and innovation initiatives for NordForsk. In recent years more emphasis has been placed on European and international cooperation.

In July 2012 NordForsk signed a Memorandum of Understanding (MoU) with the European Association of Research and Technology Organisations, the League of European Research Universities, the European University Association (EUA) and the European Commission. The purpose is to strengthen and assist the realization of the European Research Area (ERA). The main focus areas in the collaboration are researcher career opportunities and mobility, gender equality, research infrastructures, open access to data and publications, and eScience.

NordForsk has launched already since 2011 a major research initiative, Nordic eScience, a large research funding programme on how future research and research infrastructures can take advantage of recent developments in ICT. Nordic registry research (covering both social and biological registries) is one of the fields in focus.

3.3.1.1 The NordForsk Report on enhanced Nordic collaboration

The subject of the report (13) was Nordic cooperation on data resources with the focus placed on existing national databases and registers established mainly for administrative purposes. However, also the
question of newly-generated scientific data was handled. The challenges were analysed from six perspectives: political, legal, ethical, organisational, technical and financial. One of the main problems to tackle is finding a way to combine registers with other research data – an area where the Nordic countries will be seeking unique collaboration methods, since there are no equivalent pre-conditions for this kind of research in the rest of Europe. Some of the main challenges identified on the organization level were:

- **scattered data resources**, both in the sense of high number of different databases/registers as well as the wide range of organisations involved in maintaining them;
- **lack of research perspective in authorities** as well as the **lack of a common language between researchers and employees of the authorities**;
- For register-based research the **difficulty to access personal data** is a specific organisational bottleneck;
- **researcher’s own hesitation towards data sharing**, despite existing supporting data infrastructures.

Of particular interest from the PARENT point of view were the findings on the policy and legal levels:

The **lack of Nordic perspective in national strategies and initiatives targeting research data resources** was seen as a main obstacle to reinforcing Nordic cooperation, since there is a risk of developing policy directives which are not aligned on a Nordic level.

From a **legal perspective** the main challenges found were **different legislation regarding mainly access to personal data in the Nordic countries and between different authorities**. There is also insecurity concerning the **revision of the EU Data protection legislation** and how it will affect the national legislation and possibilities for register-based research. The work in the legal area has been taken forward by the preparation in 2013 of country studies on the Nordic legal framework (unpublished draft). The overall picture that is emerging from this study is the following:

- In all Nordic countries there are remote data access systems in place or in the making
- The role of national statistics authorities appears to be central (or moving in that direction)
- Access to data for researchers from other countries is not straightforward or uniform;
- Rights of researchers depending on their career stage may be different (e.g. researchers during their basic or PhD studies may have fewer opportunities to access data).
- The role of ethics committees and their granting permissions requires clarification.
- The relation between social sciences and healthcare/medical data must be clarified (understanding, definitions, overlaps).

### 3.3.2 The NORIA-net on Registries

NORIA-net (14) is a coordination activity for the national and Nordic research funding agencies and policy makers, funded by NordForsk. It allows identification of areas of national priority that can be strengthened through Nordic cooperation. The results of a NORIA-net will either be directed towards the development of a common research policy for a given area - with possible joint Nordic initiatives in research policy and research funding - or the preparation of specific programmes and calls for proposals.

NordForsk has initiated the “NORIA-net on Registries” (15) with the aim of increasing the utilization of the unique data registries and biobanks in and between the Nordic countries, and thereby strengthening Nordic cooperation on registry-based research. The NORIA-net should map and identify where there is added value to cooperate at the Nordic level and give strategic advice to NordForsk on how to strengthen Nordic research by increased joint use of registries. Activities within the NORIA-net have the aim of increasing coordination and accessibility of registries to the different research communities, mapping national workplans, as well as investigating potential limitations (legal, ethical, political etc.) impeding
cooperation and proposing ways to overcome these. Coordination activities targeting statistical authorities, data inspection boards and ethical committees are foreseen. The NORIA-net arranged a high-level workshop in March 2013 which, under the title “Responsible Data Sharing Across Borders” focused on how to make Nordic register data available and possible to use by a broader research audience. Significant emphasis was placed also on the need to extend the field of collaboration into including both biobanks and social science repositories and to proceed in a joined planning and implementation of the necessary research infrastructures. In the context of discussing remote access systems for researchers, which all Nordic countries either have or are in the process of developing, the importance of preserving public trust in public authorities handling sensitive personal data was once more in the foreground.

The conference Joint Nordic Focus on Research Infrastructures – Looking to the Future was held in November 2013 as part of the activities of the Swedish chairmanship of the Nordic Council of Ministers. The two-day conference focused on three subject areas of research: Climate & Environment, Health & Welfare and Materials & Molecules. In addition, two interdisciplinary themes addressed issues relating to all research infrastructures, namely e-Science/e-Infrastructure and Training/Education for research infrastructures. The outcome was a set of “Mission Statements”, one for each of the conference topics. The Action Points adopted under the Health and Welfare track included the following:

- Simplify Nordic research support operations carried out by Nordic bureaus of statistics, national health registry institutes and other registry hosting bodies.
- Set up procedures of mutual recognition for ethical review permissions between the Nordic countries.
- Support approximation of Nordic legislation and practices for using personal data in cross-border research.
- Support the development of technical solutions that enable secure transfer, storage and access to research data across borders, possibly through the Nordic e-Infrastructure Collaboration (NeIC).
- Investigate the possibility of creating a unified data sharing facility in each country, such as the Danish solution on health data.
- Launch funding schemes for research pilots and training programmes aimed at using joint Nordic data sources.
- Set up a Nordic initiative to support, monitor and develop registry-based research.

The NORIA-net on Registers and Biobanks summarized and concluded its work with the publication of the NordForsk Policy Paper Joint Nordic Registers and Biobanks. A goldmine for health and welfare research, in December 2014 (16). In the report, proposals were presented on how to overcome existing obstacles impeding Nordic data sharing, as well as ways of enhancing coordination to strengthen Nordic register-based research.

### 3.3.3 The Future Nordic Co-operation on Health

In the seminar “The Future Nordic Co-operation on Health” (February 2015,) the proposals presented by the former Swedish minister Bo Könberg as proposals for co-operation implementable within a horizon of 5 to 10 years were discussed at length (17). Among the 14 proposals, the following topics were included – all of them of relevance for PARENT JA: Highly specialized treatment co-operation, Rare diagnoses network, Public Health and Inequalities, Patient Mobility, Co-operation on eHealth, Pharmaceutical co-operation for greater cost-effectiveness and better safety, Register-based research.

In his introduction to the report, the author concluded that there is a widespread perception that Nordic countries should co-operate more and better with register-based research. An additional worthwhile remark is his direct emphasis on the importance of not only Nordic, but also European collaboration, by acknowledging that in addition to pondering which health care issues will be managed better through Nordic co-operation “…an assessment must also be made of what could be managed even better at European level”.


Regarding Registry research, the report included three proposals: Strengthen collaboration in registry research, biobanks and clinical research. Develop a model for mutual recognition of ethical reviews of Nordic research projects; Set up a Nordic virtual centre for register-based research.

In the respective dedicated seminar session, participants debated on what is the source of real added value generated by registries’ data, as well as on what must be the first issue to focus on - the processes for obtaining data (e.g. ethical evaluation and applications for research use data access and use) or the data infrastructures and related issues (e.g. centralized data repository vs. the use of distributed databases?) Registry holders and science policy makers’ views are conflicting: obtaining permits take times and data usage rates go up, even though the principles of open data are being highlighted at the same time. It is important to further investigate the use of information cost models and their durability (also in the context of open data strategies). Data timeliness and relevance are of the essence. Moreover, the planning should also include electronic medical records’ data. Some proposed that metadata documentation has to be improved, so that the complexity and the diversity of registry materials is made visible to users and not necessarily invest in harmonizing the content of the registries.

Nordic co-operation progress is heavily dependent on how far the national-level solutions, as well as their implementation have gone. Everyone should invest in developing its own land registry data infrastructure and operating environment while pursuing and supporting opportunities for cooperation. In order to sustain decision-makers’ and society’s confidence in registry studies the focus must remain on achieving relevant and useful results, as well as to identify the type of studies that need to be implemented as a collaboration among the Nordic countries.

Even though conditions, approaches and priorities among countries differ when we widen the lense to include all EU Member States, the direction mapped by the Nordic countries can easily be extrapolated to an EU-wide vision roadmap – even though the pathways to implementation will differ.
4 Data Protection: revision of the EU legislative framework

The European Union last updated its data protection legislation in 1995. In 2010, the European Commission presented a communication to the European Parliament and the Council entitled "A comprehensive approach on personal data protection in the European Union", which was welcomed by both institutions. In January 2012 the Commission presented its proposal for a new Data Protection legislative framework, thus launching the process of revising the current Data Protection Directive (95/46/EC). The proposal included two statutes: General Data Protection Regulation and Data Protection Directive. As the proposed general data protection regulation will be binding for all Member States and will affect the domain of patient registries and health data in general, it is beneficial to briefly outline the situation at the start of the process and the focal questions arising through it.

The procedure of handling the Data Protection Package follows the ordinary legislative procedure, which means that the regulation has to be adopted by both the European Parliament (EP) and the Council. If the Council and the EP reach agreement on the proposal at first stage (first reading), the proposal can be adopted at that stage. If there is no agreement the procedure continues.

During the first stage, the EP chose the Committee of Civil Liberties, Justice and Home Affairs (LIBE) as the responsible committee. The task of drawing up the committee’s draft report was entrusted to rapporteur Jan Philipp Albrecht whose draft report was published on 8.1.2013. Altogether the Albrecht report proposed 350 amendments to the regulation proposal, although Albrecht supported the regulation as a legislative tool. The proposed amendments were of significance for the field of patient registries as well, since several touched on articles related to the use of health data (Article 81) and statistical and scientific research purposes (Article 83).

Albrecht’s draft report would emphasize the role of consent when handling health and other sensitive data. The draft report proposed however that Member States law could provide exceptions to the requirement of consent with regard to research that serves exceptionally high public interests, if that research cannot possibly be carried out otherwise. The data in question should be anonymised, or if that would not possible for the research purposes in question, pseudonymised under the highest technical standards, and all necessary measures should be taken to prevent re-identification of the data subjects. Such processing should be subject to prior authorisation of the competent supervisory authority, in accordance with Article 34(1).

The full Parliament confirmed the committee’s texts in a vote on 12 March 2014, thus adopting amendments to Articles 81 and 83 that would restrict the use of personal data for scientific research purposes without specific consent. In turn, the Council eventually arrived at a common position on the EU data protection regulation on 15 June 2015, thus enabling the start of Trialogue negotiations with a view to reaching overall agreement on new EU data protection rules.

The Council supported the European Commission’s initial proposal, presented in January 2012, which would allow certain personal data to continue to be used for research purposes. Research organisations indicated their support to the Council of Ministers’ suggestion that the proposed EU data protection regulation should include exemptions for research. Through the Wellcome Trust (which in turn forms part of the European Data in Health Research Alliance, bringing together academic, patient and research organisations) position statements were issued and signed by tenths of research organisations in May and October 2015.

Finally, on 16 December 2015, representatives for the European parliament, the Council of Ministers, and the European Commission agreed on a common text. Following political agreement reached in the trilogue, the final texts will be formally adopted by the European Parliament and Council at the beginning 2016 and are expected to replace national legislations on data protection by 2018.

Negotiations towards the end focused on requirement for pseudonymisation for research databases, and withdrawal from the generally extensive rights for individuals to get information, access, right of correction,
and right of deletion from databases. It is estimated that the outcome will make it possible to preserve and use data for important health and other research purposes, and will allow continued mandatory collection of data by competent health authorities to the extent legally permissible by current practices also in the future.

### 4.1 APG relevant work

Among the PARENT APG participants, EPIRARE and EUBIROD have focused their attention on issues around data protection, while the eHealth Governance Initiative has also addressed trust and acceptability. With regard to Data Protection Legislation in the EU, first EUBIROD and more recently EPIRARE have confirmed the difficulty created by the divergent national regulations in sharing health data for medical research and public health purposes. In addition, they have pointed out the tensions created in this area by the differing needs of the various stakeholder groups.

EUBIROD has identified similar types of problems with regard to the anonymization of data, one of the main means for ensuring data confidentiality. There is no unanimous definition of anonymization, and eventually each Member State is left to choose or develop its own, with all the problems such a situation signifies. A concrete proposal arising from EUBIROD in order to promote the needs of research was a targeted action of a regulatory body proposing practical solutions to reconcile the needs and expectations of investigators with legal obligations.

EUBIROD also identified a number of key areas of concern in the implementation of privacy principles across Europe, which in our view should also be investigated through the work of PARENT Joint Action.

- heterogeneity among registers (consent vs. not, data linkages, access to personal information from other databases)
- different management approaches may affect the completeness of the information in registers and comparability of results
- disclosure and disposition of personal information
- individual access to personal information
- consent
- use and accuracy of personal information

The views expressed by the eHealth Governance Initiative in their “Discussion paper on implications of the proposed general regulation on data protection for health and eHealth” confirm the centrality and importance of these issues, but do not really provide a means for addressing the problem. Below follow the main points of the Discussion paper:

**Three over-riding principles in data protection**
- all individuals in EU enjoy a consistent level of data protection and rights
- right balance between medical needs and the protection of privacy
- data protection legislation should be seen as a vehicle to facilitate the safe transfer of data for eHealth

**Definition of personal data may vary according to the scope, interests or applicable standards**

**Research**
- Data protection legislation allows the secondary use of data for research purposes
- Research should be made with anonymous data

**Consent**
- Explicit consent and vital interests are used as the legal basis for the transfer of data
- Practical and proportionate procedures for obtaining and recording consent are needed

Anonymisation
- Consent has significant cultural variations across Europe
- Personal health data vs. information (extracted from care records)
  - Information should be anonymised
  - Secondary use should be justified
- Scientific research sources should be anonymised
- eHGI submits that definitions should be appropriately reviewed to ensure alignment with concepts, current usage and the needs of the diverse eHealth stakeholder community
  - Anonymisation and pseudonymisation (rapid technological evolution going on)
    - Definitions should be set out clearly in the legislation

WP6 of the eHealth Governance Initiative has selected four key areas that it considers should be prioritized as central to trust and acceptability. One of these areas is Information Governance (Ethical and Legal), where also the topic of “...level of consent required for “secondary use” is included:

“...When information relating to patients is further used for statistical analysis, management purposes, and then stored on servers operated by third party organisations, more informed consent is needed. It can be argued that the further the information moves from the original consultation, and therefore from the purpose for which it was collected, the more specific is the level of consent required”. 
5 Registries in support of Cross-Border Directive implementation: Potential scenarios of cross-border registry data utilization

The primary focus of PARENT as identified by DG SANCO and the EAHC (based on the respective communication to the Joint Action Coordinator of 05.07.2012 following the project’s kick-off meeting) should be in the area of products:

»…advise the Joint Action partners to concentrate on a limited number of registries purposes, such as the one identified by the Commission in the preparatory process(namely to support market access and surveillance with the focus on pharmaceutical and medical devices sector’s legal requirements, health technology assessment and pricing and reimbursement).«

The use of scenarios has been an approach with a two-fold purpose. On the one hand, the scenarios link us to concrete real-life examples where the concepts and tools developed by PARENT can be tested and improved. On the other hand, for WP6 they serve as the means for exploring the question of the role of registries as supportive structures in the implementation of the Cross-border healthcare Directive.

In the following section we inspect each of the two scenarios (pharmaceutical and medical devices) from the following perspectives:

1. Focus of the scenario and potential collaborators
2. Related legal documents and policy framework
3. APG existing publications and deliverables (links to PARENT JA; identified policy related issues and proposed possible solutions).
5.1 Scenario 1a. Products - Pharmaceuticals

The aim of the Medicinal Products (pharmaceuticals) scenario was to investigate requirements for supporting cross-border comparisons based on HTA methodology, address conditional reimbursement, pricing and possibly pharmacovigilance data needs with the purpose of supporting MS and EC decision making process in these areas (use of real world data in the context of post-marketing surveillance for clinical, financial and comparative effectiveness). The areas of rare disease, diabetes, chronic illness form some of the candidate application domains.

5.1.1 Policy/Regulatory Framework: Pharmacovigilance and the role of registries

All medicinal products for human use in the European Union (EU) are strictly tested. The assessment of medicinal products quality, safety and efficacy is always performed before they are authorized for marketing. Once a medicinal product has been authorized, its safety and efficacy continues to be monitored. The purpose is to prevent, detect and assess adverse reactions to medicinal products even during their post-authorization phase. This safety (and efficacy) assessment and monitoring of medicinal products for human use is called pharmacovigilance.

Pharmacovigilance is a policy domain that is largely regulated on the EU level. In 2010 the medicinal issues domain was transposed from DG MARKT to DG SANCO. New pharmacovigilance legislation that amended existing legislation (Directive (2001/83/EU) and Regulation ((EC) No. 726/2004) was adopted by the European Parliament and the Council of Ministers in December 2010. The new legislation consists of a Directive (2010/84/EU) and a Regulation ((EC) No 1235/2010). Most of the new legislation had to be implemented within 18 months of becoming law or latest by July 2012. However, e.g. Finland was able to revise its own legislation only in February 2013.

The legislation is accompanied by the implementing regulation ((EU) No 520/2012), published by the European Commission in June 2012. The implementation regulation is a binding act in its entirety and is directly applicable in all Member States. It provides details on the operational aspects of the new legislation. Furthermore, at the end of 2012 legislation was again amended in the form of a Directive and a Regulation. On 27 October 2012 the new Pharmacovigilance Directive (2012/26/EU amending Directive 2001/83/EC) and on 14 November 2012 the new Regulation ((EU) No 1027/2012 amending Regulation 726/2004) were published. These very recent amendments and changes must be implemented already during the year 2013. The Directive must be implemented into national law by October 28, 2013. The Regulation will apply directly in all EU Member States from June 5, 2013.

The objectives of the updated legislation include:

- Proactive and proportionate risk management
- Higher quality of safety data
- Stronger link between safety assessments and regulatory action
- Strengthened transparency, communication and patient involvement
- Clear tasks and responsibilities for all parties (MAH, competent authorities, EMA)
- Improved EU-decision making processes (harmonized decisions and efficient resource use)
- Establishment of Pharmacovigilance Risk Assessment Committee.

The main focus of the amendments in the Pharmacovigilance legislation has been the reduction in the number of Adverse Drug Reactions (ADRs). This can be seen in several measures imposed by new legislation. One central sphere is the recognition of post-authorization safety and efficacy studies (PASS, PAES).

Post-authorization safety and efficacy studies are studies which are undertaken after a medicinal product has been authorized. The purpose of these studies is to provide more information on the safety and efficacy of the product within the authorized indications. The purpose of the information in these study
forms is to support regulators in decision-making on the safety and benefit-risk profile of medicines (EMA, 2012a.). As such, post-authorization safety and efficacy studies have already been conducted. The aforementioned legislative amendments have, however, introduced a new approach to the use of PASS and PAES by making them formally recognized. The marketing authorization holders can be obliged to conduct such studies by imposing that obligation as a condition to the marketing authorization. Moreover, competent authorities may require the performance of such studies even after the authorization, if new scientific evidence indicates that previous efficacy evaluations might have to be revised significantly. EMA has begun its implementation in 2012 by giving guidelines on good pharmacovigilance practices (GVP).

5.1.2 Post-authorization safety studies –PASS

According to EMA (2012) "PASS is a study of an authorized medicine which identifies, characterizes or quantifies a safety hazard, confirms the safety profile of the medicine, or gauges the effectiveness of risk management measures during its lifetime."

According to the implementing regulation, where competent authorities have concern as to the safety of a medicinal product, they should be able to impose on marketing authorization holders the obligation to conduct post-authorization safety studies ((EU) No 520/2012, Recital 16). Chapter VIII defines Post-authorization safety studies and applies to non-interventional post-authorization safety studies initiated, managed or financed by a marketing authorization holder under obligations imposed by a national competent authority, the European Medicines Agency or the Commission in accordance with Articles 21a and 22a of Directive 2001/83/EC and Articles 10 and 10a of Regulation (EC) No 726/2004.

5.1.3 Post-authorization efficacy studies PAES

According to EMA’s definition “A PAES aims to clarify the efficacy for a medicine on the market including efficacy in everyday medical practice.” (EMA 2012)

According to directive 2001/83/EC Article 22a after granting marketing authorization, the national competent authority may impose an obligation on the marketing authorization holder:

(a) to conduct a post-authorization safety study if there are concerns about the risks of an authorized medicinal product. If the same concerns apply to more than one medicinal product, the national competent authority shall, following consultation with the Pharmacovigilance Risk Assessment Committee, encourage the marketing authorization holders concerned to conduct a joint post-authorization safety study;
(b) to conduct a post authorization efficacy study when the understanding of the disease or the clinical methodology indicate that previous efficacy evaluations might have to be revised significantly. The obligation to conduct the post-authorization efficacy study shall be based on the delegated acts adopted pursuant to Article 22b while taking into account the scientific guidance referred to in Article 108a.

The imposition of such an obligation shall be duly justified, notified in writing, and shall include the objectives and timeframe for submission and conduct of the study.

The European Commission is empowered to adopt a delegated act laying down the situations in which post-authorization efficacy studies may be required. The preparation of delegated act is now in process. The Commission has prepared a reflection paper which was rolled out for public consultation. The period of consultation ended on 18 February 2013.
5.1.4 APG related work

From the APGs reviewed, EPIRARE has identified topics relevant for this area of policy making, more specifically in the context of Orphan Medicinal Products (OMP) (18). Because of the specific features of OMPs and the small population of patients for whom they are developed, the application of pre-marketing drug development protocols is difficult. For these medicinal products, therefore, the acquisition of safety, effectiveness and appropriateness data after marketing authorization are of special value compared to that of other drugs. The fact that OMPs are often developed by SME, rather than large pharmaceutical companies is also aligned with the EU industrial policy.

The platform proposed for rare diseases by EPIRARE would aim to provide support to post-marketing assessment, and to identification of patient populations for clinical trials. It would also function as the host of an alert network for pharmacovigilance, support post-marketing assessment and provide the basis for collaborating with European Reference Networks.

WP5 of the EUnetHTA Joint Action 1 has addressed in one of their reports (19) the methodological issues pertinent to relative effectiveness assessment of pharmaceuticals – a task they took up as a follow up to the work completed by the High Level Pharmaceutical Forum. In the context of preparing the report, they collected data on national approaches to relative effectiveness assessment through a survey in 30 jurisdictions (26 European jurisdictions, Australia, Canada, the USA and New Zealand). They found that except for the USA, all jurisdictions surveyed perform evaluations that include a comparative analysis of efficacy and/or effectiveness of pharmaceutical(s) in comparison to alternative(s) to feed national reimbursement decisions on pharmaceuticals. The methodological approaches used for rapid and full assessments do not differ much. The main differences seem to be the number of comparators (more comparators for a full assessment) and the timing of the assessment. The rapid assessment is often done after market authorisation whereas a full assessment is often performed when the pharmaceutical(s) is/are on the market for a number of years. Relative effectiveness assessments (broadly defined), amongst other criteria, are always considered by national decision-makers when making reimbursement decisions.

What is of particular relevance for PARENT are the various sources of data used in these assessments, their assumed validity and frequency of use for the specific purpose. Here is an overview of the EUnetHTA survey findings:

- Multiple sources are used for the assessment: manufacturer reports, expert knowledge, guidelines, other HTA reports, literature, European Public Assessment Report/National Public Assessment Reports
- Unpublished (raw) clinical data are at least sometimes used in almost 80% of the jurisdictions and confidential data are at least sometimes used in about 60% of the jurisdictions for assessments
- Other sources: national pharmaceutical consumption statistics, external reports and web-based study registries
- There is some divergence between jurisdictions whether unpublished clinical data and/or confidential data are used.

Sources used to determine the comparator in the assessment

- Multiple sources are used for the identification of appropriate comparator(s) (often the assessment body identifies the appropriate comparator)
  - product sponsors, experts, clinical guidelines, methodological guidelines
  - epidemiological data about treatments, list with reference groups, published literature and assessment by other HTA agencies.
5.2 Scenario 1b. Products – Medical Devices

Safety (& optionally Market Access): the aim of this scenario was to support cross-border identification of adverse events (outliers) and connect them to specific products in order to support the establishment of a potential alert mechanism. From a clinical content perspective the scenario would cover medical devices (20, 21), in particular implants for arthroplasty. Clinical content was provided by the European Arthroplasty Register (EAR).

The focus of the EAR proposed scenario was on Exchangeable Neck Implants. Hip implant stems with exchangeable necks were introduced some years ago. Data from the Australian Arthroplasty Register indicate a safety problem. Only these data and data from the British National Joint Registry are available for an assessment at present. There are sufficient data for an ad hoc analysis available in Europe, according to a quick survey in Italy (Emilia Romagna, Lombardia), Spain (Catalunya), Great Britain, Finland, Slovakia, Slovenia, and Portugal, possibly also in the Netherlands. The scenario tested the ability of these registries to provide real setting safety data, thus utilising the cross-border secondary usage potential of patient registries (see WP4 Report on the Arthroplasty Scenario).

5.2.1 Policy/Regulatory Framework: Medical Devices directive and the role of registries

There is a recognized cross-border need to identify Medical Device adverse events and connect them to specific products. In the winter of 2013 the European Commission’s Scientific Committee on Emerging and Newly Identified Health Risks requested an opinion on the safety of metal-on-metal joint replacements with a particular focus on hip implants and for an updated scientific opinion on the safety of PIP silicone breast implants. The recent metal-on-metal-implant and PIP-implant performance concerns have led to debate about the adequacy of the current regulatory tools to assess medical devices. As there are growing expectations for utilizing more post market data of medical devices, also registries and their relevance has become a topic to be studied.

Medical devices cover a wide range of products. The use of registries varies between different products. Especially in the field of implantable products there is an already well-established tradition for registries. These registries focus on device-specific areas such as orthopaedic implants or cardiovascular devices and collect data on patients who have been exposed to a specific device. In addition, post-approval observational real-world studies are conducted. The competent authorities have their regulatory means to track and study products used in the market.

According to Glicklich et al. (22) patient registries can be used for variety of purposes regarding medical devices including effectiveness research, post-marketing commitments or safety monitoring, surveillance programs and quality improvement programs. As much detail about the device should be gathered to ensure its accurate identification. Registries should contain sufficiently detailed patient, device and procedural data, and be linked to meaningful clinical outcomes.

In the field of medical devices traditionally, and by legislation, post-marketing surveillance is performed through spontaneous adverse event reporting to competent authorities from users and industry, covering instances of injuries, deaths and malfunctions. The exact requirements for spontaneous reporting depend upon the approval type, and product type. Spontaneous reporting, however, captures only a small part of the actual adverse events. There is a legitimate concern that important data of adverse events does not reach authorities and manufacturers in a timely manner. Also FDA’s report (23, 24) on Medical devices states that the notable limitations of passive surveillance systems are the potential submission of incomplete or inaccurate data, under-reporting of events, lack of exposure data, and the lack of report timeliness.
5.2.1.1 EU legal and regulatory revisions


The proposed regulation would replace the Directive 90/385/EEC regarding active implantable medical devices and Directive 93/42/EEC regarding medical devices (MDD, Medical Device Directive). A proposal for the Regulation of in vitro diagnostic medical devices would replace Directive 98/79/EC regarding in vitro diagnostic medical devices (IVD directive). In July 2013 the legislative package is in the process of the Committee Environment, Public Health and Food Safety. Rapporteur Dagmar Roth-Behrendt gave a Draft Report on the proposal in April 2013. The regulations still might change as more than 900 amendment proposals have been added by the Parliament. The ENVI Committee is likely to vote on the legislation in September 2013. According to the Commission, certain focal aims of the legislative reform are to tighten the requirements for clinical evidence, to ensure patient and consumer safety, and better traceability of devices throughout the supply chain, enabling a swift and effective response to safety concerns. Article 83 of the proposal states that the Commission and the Member States shall take all appropriate measures to encourage the establishment of registers for specific types of devices to gather post-market experience related to the use of such devices. Such registers shall contribute to the independent evaluation of the long-term safety and performance of devices.

The Commission proposals were accompanied by an impact assessment documents on the revision of the regulatory framework. In the Commission Staff Working Document (25) the level of harmonization of the Post-market safety (vigilance and market surveillance) of medical devices in Member States is stated as a focal problem. For example, the manufacturers do not report serious incidents to the competent authorities according to the same criteria in different Member States. However, the methods of gathering post-market safety information are not widely reflected in the Impact Assessment document. Although observational studies or registries are not reflected as such in the texts, the following objectives were presented for the legislative framework that might have particular significance from the point of view of registries: Enhanced legal clarity and coordination in the field of post-market safety, enhanced transparency regarding medical devices on the EU market, including their traceability, enhanced involvement of external scientific and clinical expertise.

As an indicator for success in the field of enhanced transparency and traceability “will be that 5 years after entry into force of the new legislation, a clear picture will be available at EU level as regards the economic operators and medical devices on the EU market and the key clinical data supporting the assessment of high risk devices.” Additionally in April 2013 the Commission gave a recommendation on a common framework for a unique device identification system of medical devices in the Union (2013/172/EU). The aim is that if Member States decide to develop their own UDI mechanisms these should be made compatible with each other and with the future UDI system of the Union. The ongoing revision process of the current Directives should empower the Commission to adopt more detailed traceability requirements.
5.2.1.2 The current EC Guidelines on Post Market Clinical Follow-Up studies

In January 2012 the European Commission gave guidelines on Medical Devices Post Market Clinical Follow-Up (PMCF) studies. According to the guidelines risks remaining after risk control measures have been taken (so called residual risks) should be investigated and assessed in the post-market phase through systematic PMCF studies. These studies are mentioned as one of several options available in post-market surveillance.

A PMCF-study is defined as a study carried out following the CE marking of a device and intended to answer specific questions relating to clinical safety or performance (i.e. residual risks) of a device when used in accordance with its approved labeling. The guidelines identify many examples of circumstances that may justify PMCF studies. The elements of a PMCF study, including the methods of the study are somewhat broadly addressed. However, it is noted that PMCF studies can follow several methodologies, such as 1) the extended follow-up of patients enrolled in pre-market investigations, 2) a new clinical investigation, 3) a review of data derived from a device registry or 4) a review of relevant retrospective data from patients previously exposed to the device.

According to Article 49 on Clinical Evaluation, manufacturers should conduct a clinical evaluation in accordance with the principles set out in the Article and Part A of Annex XIII. A clinical evaluation should follow a defined and methodologically sound procedure based on any of the following:

(a) a critical evaluation of the relevant scientific literature currently available relating to the safety, performance, design characteristics and intended purpose of the device, where the following conditions are satisfied: it is demonstrated that the device subject to clinical evaluation and the device to which the data relate are equivalent, and the data adequately demonstrate compliance with the relevant general safety and performance requirements;

(b) a critical evaluation of the results of all clinical investigations performed in accordance with Articles 50 to 60 and Annex XIV;

(c) a critical evaluation of the combined clinical data referred to in points (a) and (b).

The clinical evaluation and its documentation should be updated throughout the lifecycle of the device concerned with data obtained from the implementation of the manufacturer's post-market surveillance plan referred. The clinical evaluation and its outcome should be documented in a clinical evaluation report.

According to the proposal’s Annex XIII on Post-market clinical follow-up (PMCF), PMCF is a continuous process to update the clinical evaluation and should be part of the manufacturer’s post-market surveillance plan. To this end, the manufacturer should proactively collect and evaluate clinical data from the use in or on humans of a device which is authorized to bear the CE marking, within its intended purpose as referred to in the relevant conformity assessment procedure, with the aim of confirming the safety and performance throughout the expected lifetime of the device, the continued acceptability of identified risks and to detect emerging risks on the basis of factual evidence.

The PMCF should be performed pursuant to a documented method laid down in a PMCF plan. The PMCF plan should specify the methods and procedures to proactively collect and evaluate clinical data. The manufacturer should analyze the findings of the PMCF and document the results in a PMCF evaluation report that should be part of the technical documentation. The conclusions of the PMCF evaluation report should be taken into account for the clinical evaluation and in the risk management. If through the PMCF the need for corrective measures has been identified, the manufacturer should implement them.
5.2.2 Medical Device Safety initiatives in the United States

Improving the safety surveillance has become a key issue also in the United States. In 2008 the U.S. Department of Health and Human Services and FDA’s Sentinel Initiative was launched. That is a long-term effort to create a national electronic system for monitoring product safety enabling the FDA to conduct active surveillance. In the Initiative the FDA is required to collaborate with public, academic and private entities. The current data model queries administrative and claims data maintained by partner organizations.

In the legislative process of the Patient Protection and Affordable Care Act a national medical device registry was envisioned established by the Department of Health and Human Services (HHS). Within the registry, devices would be listed by type, model and serial number, or some other unique identifier. The registry was intended to assist the HHS in evaluating the safety and effectiveness of all implantable medical devices, including all orthopaedic implants. Ultimately the registry was not included in the final version of the Act. However, FDA has been active mapping the strengthening of medical device safety.

The US Food and Drug Administration’s Center for Devices and Radiological Health has proposed four specific actions, using existing resources and under current authorities, to strengthen the medical device post-market surveillance system in the United States. These proposals were presented in a report given in September 2012 and updated in April 2013 (23, 24) after workshops for stakeholders.

According to the FDA report “a medical device post-market surveillance system should quickly identify poorly performing devices, accurately characterize and disseminate information about real-world device performance, including the clinical benefits and risks of marketed devices, and efficiently generate data to support premarket clearance or approval of new devices and new uses of currently marketed devices.”

The report recognizes that the vision for strengthening the post-market system can only be achieved with active participation of many other key domestic and foreign stakeholders such as the industry, health care providers, patients, academia, third-party payers, hospitals and other healthcare facilities and other government agencies.

Four key strategic actions are presented: 1. establishing a Unique Devise Identification System and promoting its incorporation into Electronic health information; 2. promoting the development of national and international device registries for selected products; 3. modernize adverse event reporting and analysis and 4. developing and using new methods for evidence generation, synthesis and appraisal.

In the field of the first pillar: Standard, unambiguous way to document device use in EHRs, clinical information systems, and claims data sources. Adoption of the UDI is essential to expanding the Sentinel Initiative to cover medical devices (e.g. query large claims data sets for patterns that may indicate safety problems, as is currently being done for prescription drugs).

In the field of the 2nd pillar the FDA is not seeking to develop a centralized repository of registry data. Each registry would retain control over its data. The FDA envisions helping in facilitating the creation of registries, but not regulating standards for registries, such as business models or taxonomy.

It is very interesting that the FDA report states that “for targeted areas, it may be more cost-effective to pursue nationwide medical device registries focused on certain product areas of high importance as reflected by a large public health need, patient exposure, uncertain long-term or real-world device performance, or societal cost. For other device areas where the benefit-risk profiles are well-understood, registries may not be needed.”
In the field of modernizing the adverse event reporting and analysis the FDA is working with the partners to explore automated adverse event reporting systems. These systems would facilitate the submission of device-related adverse events and minimize the effort required by the reporter. Additionally they aim to increase the number of adverse event reports received electronically, develop a mobile application for adverse event reporting, modernize the medical devise adverse event database and rapidly identify safety signals using automated, computerized statistical methods to discover signals in large databases.

In the updated version of the strategy paper FDA states that “the creation of individual registries to meet the needs of a specific manufacturer or a specific product historically has been neither efficient nor economical, and it is impractical and unnecessary to have registries for every medical device type. Instead, targeted registry efforts should be based on wide stakeholder input and support and should focus on selected areas of high importance as reflected by a large public health need, patient exposure, uncertain long-term or real world device performance, or societal cost.”
6 Proposals for Policy Actions – Current insights

The overall objective of the PARENT Joint Action has been to support EU Member States (MS) in developing comparable and interoperable patient registries in fields of identified importance (e.g. chronic diseases, medical technology) with the aim to rationalize the development and governance of patient registries, thus enabling analyses of secondary data for public health and research purposes in cross-border settings. Our activities throughout the JA have been driven by the conviction that to truly achieve this goal we need to improve not only the ability of patient registries to share data, but also improve the process of feeding data to the registries from their primary sources such as Electronic Health Records (EHRs).

The European Commission, as well as the majority of EU Member States have labored persistently for over two decades towards the introduction, implementation and networking of EHR systems and eHealth services on the national and cross-border level. The role of policy has been instrumental in the considerable progress that has been achieved. The two eHealth Action Plans (of 2004 and 2012) and other related Commission Communications, the eHealth conferences, forums and events, supported through a series of projects implemented by utilizing the whole spectrum of Community funding instruments have ensured a steady momentum and constant steps forward.

From the point of view of PARENT objectives what has been a major gap in this effort is the inadequate attention to the secondary use of health data, with efforts centering on the production, documentation and exchange of data around and for the purposes of professional-patient interaction. The approach underlying eHealth services development thus far is organized vertically (see Fig. 4) and thus not adequate any more in the new Digital Europe environment, Big Data analytics and the emerging culture of Learning Health Systems (31).

PARENT’s vision of the eTrajectory for health data (depicted in Figure 5) calls for the application of the EIF in a broader scope than the one it has been viewed in until now (e.g. Antilope, epSOS), to include patient registries and the potential users of their data. In the lifecycle of health data capture and use for various purposes we have to start with the end in mind and take steps to support these eventual needs by supporting the introduction, development and adoption of systems which will allow the ‘capture once – use many approach’.

Figure 4. Vertical view and approach on health data collection and use
Similar concepts have been proposed and explored from other projects and groups on both sides of the Atlantic \cite{32,33}. The main difference is that PARENT has a cross-border focus, it addresses the needs of public health and healthcare system performance (rather than e.g. clinical trials) and takes place in the context of an overall supporting policy and research trend in the EU. Our claim is that the circumstances provide us with the opportunity for realizing this vision and the role of policy in supporting this ambition is crucial.

The 3rd Health Programme Regulation \cite{34} has put forward a set of priorities, which have provided a clear direction in the process of crystalizing the PARENT policy proposals’ objectives and related actions. These priorities are:

- fostering a health information and knowledge system contributing to evidence-based decision making
- further development of standardised health information and tools for monitoring health, collection and analysis of health data
- reduce duplication of efforts and increase value for money
- contribute to innovative, efficient and sustainable health systems

PARENT has respectively put forward three objectives and the corresponding actions needed on the policy level for the objectives to be achieved.

### 6.1 OBJECTIVE 1: Creating a digital infrastructure supporting public health & medical research

**Action: Interoperable patient registries’ on the eHealth agenda**

When it comes to interoperability requirements for cross-border registry operations, PARENT places particular emphasis on the political level. The particularity of this level is that it balances between the EU and the national/regional level. EU-policy provides the direction and vision, as it has successfully done until now, but these have to be translated in the strategies and decisions made and promoted on the national/regional level.
As demonstrated by the red arrow line on the left of Figure 6, the critical aspect is that decisions made on the policy level should impact on both development of research infrastructures and eHealth strategies in ways that are conducive to and supportive of the needs of cross-border registries operations.

**Fig 6: PARENT (interoperability) requirements for cross-border registry operations with emphasis on the political level (red arrow).**

The creation, maintenance and development of registries, as well as their preparedness for cross-border operations is largely dependent on the positioning (or lack thereof) of health data resources in national strategic prioritization regarding *scientific data resources and research infrastructures*. Examples of the topics and areas that are defined on national & regional level include:

- **eScience strategy**: data resources and research infrastructures
- **eHealth strategy**: Electronic Health Records, semantics
- **Registry holders’ preparedness & resources**: Organisational & legal issues

The work of PARENT in analyzing Health Data strategies as well as patient registry holders’ attitudes and perceptions towards cross-border collaboration has revealed several shortcomings in these areas. Not all Member States have addressed relevant topics in their strategies, neither is the link between the areas of eHealth and eScience established regionally and nationally. Horizontal work and collaboration is increasingly needed on all levels. Of the registry holders responding to PARENT’s surveys, only 40% indicated that they are utilizing electronic means of data collection and for many cross-border collaboration is simply not part of their culture and way of thinking.

On the positive side, important areas of convergence have been identified:

- Similar type registries are established (in terms of content focus) in most MS as the basis of national health information systems
- Strategic aim of connecting EHR data and registries appears in many national strategies.
- Research as a theme *and* as an economic driver for public health cost savings and enterprise development opportunities
- Links to biomedicine and biopanking are also mentioned in some national strategic priorities.
Making it happen

The challenge in bringing forward this objective will be the fact that at any point in time, different MS are usually at differing stages of progress and levels of awareness. Nevertheless, at this time when many MS are either developing new infrastructures or updating their existing ones both in the areas of eHealth and biomedicine/biobanks there is an excellent opportunity for alignment of joined planning and implementation. Infrastructures and solutions for remote use of health (and other) data are an area where significant work is in progress (such as, e.g. the Data Without Boundaries project). The outcome of these efforts will play a central role in defining the landscape in which also the solutions for cross-border use of registry data will come to operate. It is therefore not sensible in terms of use of resources and sustainability to develop self-standing solutions. Just as in many cases before, healthcare will need to adapt to a broader environment. It is nevertheless important to identify and ensure the implementation of any potential special needs pertaining to registries.

The engagement of MS to drive national and regional strategies and implementation efforts will be crucial to success and the role of EU-level direction and coordination will be decisive, such as e.g. through the eHealth Network and JAseHN, other bodies, funding channels.

6.2 OBJECTIVE 2: Access to better and safer healthcare for Union citizens

**ACTION: Promote patient registries’ as tools for ERNs and rare disease services & research**

The analysis of the Directive as well as of the progress of its transposition and implementation by Member States (see Chapter 2.5) has demonstrated that the process of cross-border healthcare services provision is still at an early phase. Nevertheless, there are exceptions to the rule such as e.g. the area of Rare Diseases and the respective European Reference Networks. The field of Rare Diseases, due to its inherent need for data sharing and collaboration has been very actively investigating for almost two decades now issues related to cross-border activities for both care and research. In the process, several target areas have been identified specifically in relation to patient registries, which can also form the content of forthcoming work:

- Fragmentation of RD registries, need for harmonization, quality processes and standardization
- Need for evidence of good quality and safe care, impact on patient outcomes
- Identified need of common services for RD - synergies with biobanks
- Reference sources for policy makers: e.g. HTA for orphan drugs and/or diagnostics

Since the start of the JA, PARENT has had close links to Rare Disease projects and ERN activities through the APG members. Particularly during the last year of operations of PARENT and thanks to an excellent alignment of views and activities with the EXPAND project and the EUCERD Joint Action, as well as the inspiring exchanges with BBMRI-ERIC and BBMRI-ADOPT projects we were actually able to take concrete **action** steps with regard to our proposal. Starting from a first identification of shared interests during the EXPAND WP3 workshop in November 2014 and following through to the EXPAND Multistakeholder workshop in January 2015, a group of dedicated experts with the support of EC policy officers prepared and presented first an **Information Paper to EC Expert Group on Rare Diseases in June 2015 (see Annex 2).** Having received confirmation that we are on the right track, collaborative work continued towards the drafting of an **Exploratory paper** (a more detailed version and plan for further steps in the collaboration), which in turn formed the background for the formation of a Task Force (Task-Force on Interoperable data sharing in the framework of the operation of ERNs) under the auspices of the newly started RD-Action Joint Action and was discussed further during the RD-ERN dedicated workshop in Lisbon in December 2015. With ERN networks having gotten a head start through their inclusion in the CEF funding programme of 2015 and the call for the first ERNs excepted in early 2016, it can only be hoped that the collaboration will be carried on and will have support also from the actors in the eHealth domain.
6.3 OBJECTIVE 3: Contribute to innovative, efficient and sustainable health systems

ACTION: Strengthen use, usefulness and suitability of registries for HTA-based patient and consumer safety and monitoring

The area of HTA and the support of its data needs through high quality registry data and processes have been an undisputable and steady target for PARENT activities and actions since the start of the project. Through a series of workshops, seminars and collaborative brainstorming, the following items have been prioritized with regard to patient registries and HTA:

- **Time-critical element in data acquisition**
  Many key HTA processes, such as for example Rapid Assessments, which can be instrumental in reimbursement decisions cannot make use of registry data collections, due to the very slow response time to data requests. Our proposal is to explore the possibility of establishing dedicated processes for HTA-needed registry data acquisition. In practice that would mean both legal and regulatory changes, as well as changes on the organizational level of registry operations. From the side of PARENT again, this is an area which should be reflected in the RoR design and processes.

- **Proactively ensure data availability**
  In addition to guaranteeing speedy availability of data which caters to HTA processes, it is equally important to ensure that relevant data will be available at the time when it is needed. HTA agencies have adopted the practice of horizon scanning for several years already. As a result, they have knowledge of upcoming technologies which may need to be assessed in the near future. Patient registries could benefit from that activity, if a feedback loop would be established between HTA horizon scanning activities and patient registries. By establishing a process of notification of registries with regard to emerging/new technologies, registry holders could ensure the incorporation of pertinent terms and codes when updating their data content, thus ensuring the presence of relevant data in their repositories at the time when HTA agencies may approach them with a data request.

6.4 The proposal for a National Contact Point for registries (R-NCP).

The idea for a National Contact Point for Registries (R-NCP) first started evolving during the PARENT Seminar in Helsinki, in June 2014. The concept was discussed and developed further in collaboration with APG members and stakeholders in subsequent meetings and workshops. The necessity for such a national hub is common in many collaborative EU-level undertakings which span Member States borders. In the context of PARENT the purpose is two-fold, connected to the dissemination, uptake and update of PARENT deliverables and tools, as well as possible future services offered through the PARENT Framework (see for more details Report D9 Sustainability of cross-border collaboration on secondary use of registry data).

The following Q&A set is intended to demonstrate the collective ideas and understanding of the purpose and role of the R-NCP, as reached by the end of the PARENT JA.

**What would be the R-NCP’s main function(s)?**
- The primary role of R-NCPs would be to function as Ambassadors of the PARENT Guidelines and other deliverables and tools in the respective Member State. It would be a dedicated body responsible for
reminding registry holders of the benefits of using the Methodological Guidelines and assisting them to do so e.g. by maintain pertinent informative web pages in the local language or languages.

- The R-NCP would be responsible for providing information, training, translation and interpretation of the European PARENT Guidelines in their respective country. The R-NCP could also utilize the PARENT Assessment Tool in local registry improvement activities. At the same time, the R-NCP would collect feedback from registry holders and other users of PARENT deliverables and tools, to be utilized in maintenance and further updates of the PARENT Framework.

- Conversely, the R-NCP would provide information on the national/regional patient registries and repositories, would maintain current knowledge of the respective Member State legislation and ethical procedures for retrieval of data for cross-border information needs. NCP’s task would be to upgrade information on the national situation in the PARENT Guidelines documentation.

- R-NCP would have as the responsibility to maintain up to date the information available in the PARENT RoR for their respective country. The NCP would either update the RoR through its representative or by guiding registries so that they can themselves refresh or supplement their respective RoR profiles. This approach by passes the problem of lack of incentives of individual registers to update the RoR. Other options to resolve the lack of incentives and activity could be:
  - Making the process obligatory (e.g. Swedish quality registries).
  - Alternatively, it could become a condition for EU funding. Becoming a member of the RoR and keeping the information up to date would form proof of maximizing the value of data that you register (maximizing its value at least on European level, using it beyond the original team who created a registry).

- NCP’s customers could be researchers from academia, research institutes, clinicians, industry, pharmacovigilance authorities, other public authorities, potentially patients.

- Stakeholders engaged with the R-NCP: Other NCP’s, the Commission, the JRC, Biobanks, BBMRI, registries and quality registries, national archives.

- R-NCP would be the focal point on data protection expertise, e.g. in cross-border data flows.

- R-NCPs would seek to dismantle barriers to cross-border sharing of health data.

**What other role(s) would the R-NCP fulfil?**

- NCP would be responsible for interoperability and the coordination of standards concerning registry activities for the country in question.

- NCP would disseminate information on eHealth, secondary use and digitalisation of data-related matters.

- The R-NCP would bring transparency to international cooperation and information dissemination.

- NCP would guide researchers / industry / authorities on how to obtain data from other Member States in cross-border data exchange and collaboration situations.

- NCP could, if necessary, provide for-fee consulting services and undertake investigations e.g. on behalf of industry, if the law would allow it.
• R-NCP could also operate as part of an organization offering data linkage and brokering services or perform such tasks itself (for an architectural proposal see PARENT D9 Report), but at least initially that would not be the R-NCP's basic idea. However, it is recommended that the R-NCP would be located in an existing "service provider".

Who would be the R-NCP host organization?
The appropriate placement for the RNCP would need to be considered on a country to country basis. In some countries, it would be natural that the RNCP would be combined with the main national biobank / registry service provider association in order to ensure efficient knowledge and understanding of the key wellbeing/welfare and health data repositories. E.g. in Denmark a natural place for the establishment of the R-NCP could be SSI (Statens Serum Institut), in Finland THL, while e.g. in Sweden a suitable location could be the national quality registry operations coordinating body. Other suggestions:
• Pharma/medical device/regulatory HTA agencies could act as some form of R-NCP.
• National Centres for Rare Diseases might be interested in playing this role, but then there would also need to be some proof of formal endorsement e.g. listing of National contact points (on PARENT’s website, EU Commission’s website).
• Overarching auditing organisations might be primary contact point, e.g. in case of the Netherlands it could be DICA (Dutch Institute for Clinical Auditing) where several institutions are involved (e.g. EFPIA, ZIN).
• Given the fact that Registries are dealing with sensitive personal data, the respective instance which deals with that issue in the country could take up the R-NCP tasks. Ministries of Health can provide a list of these organisations.

How many R-NCPs would there be per Ms?
R-NCP would be, as its name suggests, at least one in each Member State, however if necessary or suitable to existing structures in the country more than one Registry-NCP could exist.

Is there a mandate for the establishment of R-NCPs?
• The mandate for considering the establishment of R-NCP would be based on the same grounds as PARENT JA: serving the purposes and objectives of the XB Directive, supporting services and research in Rare Diseases, European co-operation on pharmacovigilance, quality & safety follow up of medical devices.

What will be the next steps in the R-NCP proposal?
• A possible strategy would be to consider and agree on what are good characteristics for an R-NCP. First, define what are the requirements that a contact point should fulfil and only then determine who will serve as the contact point (who is willing and able to fulfil these requirements). Models which should be considered include: National Registry research support centers, BBMRI Nodes / Hubs. The ‘co-habitation’ of registries and biobanks services is a sensible prospect to consider, given the growing integration between the two infrastructures.
• Clarifying the relation and possible collaboration or integration between the eH-NCP and the R-NCP. JAseHN will follow up on the proposal made by PARENT to establish National Contact Points whose role would possibly be to serve as a reference point for registry holders collecting information on the
registries and disseminate Parent guidelines. It is to be determined if eHealth NCP could take over these tasks. (For a fist mapping exercise on the level of governance, see D9 – D9 Sustainability of cross-border collaboration on secondary use of registry data)

7 Conclusions and Future prospects

The period of activities of PARENT Joint Action coincided with a particularly active, dynamic and productive period in the EU digital health landscape. The components of the necessary infrastructure were explored, developed, tested and implemented in numerous important projects, some completed, others still ongoing (such as epSOS, Antilope, SemanticHealthNet, ASSESS-CT, EXPAND – to just name a few). The work undertaken is focused on creating the prerequisites for interoperable cross-border eHealth services, addressing all layers of the European Interoperability Framework.

![EU Coordination Landscape](image)

Fig. 7 – The EU cross-border registry collaboration environment

PARENT JA has succeeded in bringing EU patient registries in the spotlight as valuable health data resources, worthwhile to be seen and understood as an indispensable part of the Digital Europe infrastructure. We have developed a clear added value proposal, the necessary tools for its implementation and a proof-of-concept version of the operational mode of the Framework.

In collaboration with the members of the PARENT APG group and a wide representation of stakeholders we have iteratively developed and elaborated in dialogue a set of actions necessary to bring forward the results already achieved. We have been fortunate to even see some of our proposals already changing into concrete action steps, such as in the area of Rare Diseases and European Reference Networks. A number of exciting continuation paths has opened toward the end of PARENT JA. Our deliverables will be tested and assessed through various projects and initiatives including:

- the forthcoming platform for Rare Disease of the EC Joint Research Center
- the pilots of the soon starting EUnetHTA JA
• the EMA Initiative for patient registries (strategy and pilot phase)
• the assessment of PARENT Guidelines through JAseHN JA
• the activities of the RD-eHealth Task Force established under RD-Action JA
• Possible R&D projects under the IMI and Horizon 2020 funding programmes.

Important experiences and feedback will be accumulated through these hands-on experiences and depending on the outcomes policy and action priorities will need to be revisited, along the rest of PARENT deliverables. The opportunities for linking the work in patient registries with the activities ongoing in the areas of biobanking and research infrastructures, as well as the new prospects opening through linking citizen and patient-collected data to patient registries are some of the prospects already visible in the horizon.

8 References

4. Council Conclusions on Common values and principles in European Union Health Systems, 2006/C 146/01
Annex 1– Iterative development of PARENT JA policy proposals - Stakeholder feedback

The policy and implementation context for cross-border patient registries

The workshop “Policy and implementation context for cross-border patient registries” was organized by PARENT Joint Action WP6 in Brussels, on March 27th. Participants discussed the interim findings of WP6 on policy analysis, European and international registries’ strategies and governance, and potential models for sustainable cross-border registry platforms. Representatives of stakeholders and collaborating partners (DG Sanco/European Reference Networks, European Social Insurers Platform, EUnetHTA Joint Action2, Health Information and Quality Authority of Ireland) provided commentary and insights, while speakers from PARENT Associated Projects Group (SemanticHealthNet, EPIRARE, EUBIROD, eHGI) presented their experiences in developing sustainable solutions.

The feedback received provides us with input for further work in view of the next round of stakeholders’ discussions culminating at the PARENT meetings in 12-13th of June, in Helsinki Finland. The intention is to inform the planning and formulation of the proposals and solutions being developed by the PARENT Joint Action – including the proposal for future maintenance of the PARENT Framework and related services.

Meeting highlights:

- Resources such as these developed by PARENT are in high demand, among others by European Reference Networks, insurers’ organisations as well as Member States. Guidance with regard to registries and management of data generally, as well as cross-border data exchange is needed, as well as tools for setting up registries (particularly in support of interoperability and data protection aspects).
- An absolute prerequisite for registry data use in Health Technology Assessment (HTA) studies is the publication of studies based on registries’ data. Use of primary registry data in HTA concerns foremost health economics analysis. Many possibilities exist for improving the HTA-registries synergy, for example the establishment of a registries early-notification process with regard to emerging/new technologies.
- The mapping of national policies concerning sharing data resources for research and developing register-based research in EU Member States has produced an initial directory of strategic policy documentation. Countries seem to progress in a stepwise fashion, from the establishment of National Health Information Systems to compilation of national health information databases inventories to exploring the requirements for data sharing across borders.
- Best case example: The Health Information Quality Authority, Ireland: HIQA has utilized the International Standard Dublin Core Metadata Template to develop a template for describing national health and social care information collections, issued Guiding Principles for National health and social care data and is presently developing recommendations on an integrated approach to national data collections.
- Registry platforms: EUBIROD’s BIRO system is a method for diabetes data collection, developed in collaboration with Member States. Although based on open source technology, which is free for utilization in other clinical areas, the system is still in search of longer term funding. SemanticHealth net, having the objective of proposing a model for a European virtual organisation for semantic interoperability is experimenting with a mix of ontologies, terminologies, information models, but will not be delivering modeling assets/archetypes. The field of rare diseases is moving a step closer to the goal of a dedicated registries platform, where the expertise of various entities such as EPIRARE, EUCERD and JRC will need to be combined and utilized in synergy.
- After the recent endorsement of the minimum patient data set, the eHealth Network is presently focusing on: ePrescription and the development of an interoperability framework for drugs and the selection of project proposals, particularly such that employ proven standards, to proceed to deployment through Connecting Europe Facility funding (PARENT being one of the candidates).
Cross-border registries at your service

The Seminar “Cross border registries at your service” organized in Helsinki on June 12th 2014 by WP6 – Sustainability and implementation of the Cross-border Healthcare Directive had the aim of presenting our initial proposals on policy-focused actions necessary for advancing cross-border use of registry data. We utilized the output of WP6 work thus far in PARENT and the feedback received by Joint Action partners, APG representatives and stakeholders during our March Workshop in Brussels, and translated it to a set of steps required for registries to function in support of policy objectives. The Seminar was organized in four parts: panel discussion, introduction of policy action proposals, group work discussion and synthesis of feedback.

Panel Presentations
- The Seminar opened with a panel discussion addressing concrete experiences with cross-border registries data utilization. M. Salokannel (representing NordForsk – the organisation under the Nordic Council of Ministers providing funding for Nordic research cooperation, as well as advice and input on Nordic research policy) discussed the preconditions which must be fulfilled in order to create a Nordic data sharing framework. It is important to note that the NordForsk initiatives take a widened scope to data, including ‘classic’ health registries, as well as biobanks and social care registries. The purpose of the task is very similar to that of PARENT Joint Action, but with a Nordic focus: identification of barriers and potential limitations impeding Nordic cooperation and proposing ways of overcoming these. Legislation and an outline of the framework have been discussed in an expert meeting in March 2013. The reform of the European Data Protection Framework and particularly the corresponding Regulation is seen as an opportunity for the Nordic countries to synchronize their data sharing practices with regard to pseudonymization/anonymization of personal data, as well as with regard to ethical review. The Noria-Net initiative on registries has proposed a series of actions aiming at streamlining and facilitating data sharing and use for research purposes:
  - simplification of research support operations of data holders; setting up procedures of mutual recognition for ethical review permissions between the Nordic countries; approximation of Nordic legislation and practices for using personal data in cross-border research as well as development of technical solutions enabling secure transfer, storage and access to research data across borders, possibly through the Nordic e-infrastructure Collaboration (NeIC).

Other proposals include the possibility of establishing a single data sharing facility in each country, launching funding schemes for research pilots and training programs aimed at using joint Nordic data sources and the setting up of a Nordic Initiative to support, monitor and develop register-based research. All of the aforementioned ideas are worth-while to scale up and examine in the broader context of all EU Member States.

- As. Professor Dr. G. Labek (EAR-EFFORT European Arthroplasty Register Coordinator) shared his experience with orthopedic implant registries and the monitoring of their safety over time. The problems encountered in the study of this topic resonate to a large extent the issues the Nordic countries have decided to tackle: National processes for acquiring access to data and interpretation; processes and workflows to use the data on the regulatory and administrative level (EU and National from other countries); decision making processes on expert level (who are the experts, who should be included?); absence of a permanent infrastructure. Dr. Labek made the case for registries’ data use in orthopedic implant monitoring by demonstrating the richness and distinct nature of data acquired through real world observations vs. the ones provided in clinical studies. The picture emerging around the safety and reliability of various products was a very different one, with registry data analysis signaling serious safety concerns. Dr. Labek also predicted a complete shift of balance between the role of registry vs. clinical study data towards 2025 and in
that context underlined the importance of stakeholder involvement and continuous quality improvement cycles.

- R. Sund (Helsinki University) took us for a closer look at the methodological problems and bottlenecks in registry data utilization. At the core of the problem sits the fact that there is no general understanding of what linkable register data means even among the researchers. Sund also underlined the difficulty of getting access to data. He confirmed the existence of varying practices among register keepers and countries and he saw in the option of remote access systems both a possibility and a threat. He indicated that harmonization of privacy regulation may help, but it should not do so on the cost of paralyzing existing good practices.

Secondary use of data means utilizing data originally collected for some other purpose. Finding a suitable compromise between the research problem at hand and the available data is challenging. The more detailed the measurements needed the more metadata is required. However, usually metadata is available only for the primary purpose of data collection and at the same time, data carries a lot of tacit knowledge that is challenging to transform. Even when on the basis of their metadata contents appear to be very similar, there are always huge differences in the details of data. As a result, researchers always need to perform tailored standardization of data for each specific purpose of use. The harmonization of data structures may help this process but there will still be a need for adequate support resources – experts on specific data sets, which are not always available. Valuable and useful experiences have been gathered in projects such as EuroREACH – Improved access to health care data through cross-country comparisons http://www.euroreach.net and EuroHOPE - European Health Care Outcomes, Performance and Efficiency http://www.eurohope.info

- Last but not least, N. Heinonen, Head of Unit of the Finnish Contact Point for Cross-Border Health Care (Finnish NCP) gave us an overview of the functions of the National Contact Point specifically from the point of view of the users of healthcare services and asked us to keep in mind the original spirit of the Directive, which was precisely to cater to citizens’ and patients’ needs in order to support their free mobility inside the European Union.

The panelists’ presentations provided the backdrop for the presentation of WP6 policy-oriented action proposals, which Seminar participants were then asked to discuss and critically assess in three break-out sessions.

**Initial Policy Proposals**

We presented to our seminar participants a first set of possible policy actions to enable the use of patient registries as tools towards achieving the goals set by the Cross-border healthcare directive.

The actions were grouped around and aimed at supporting a set of three Objectives, emerging from the policy analysis of WP6 throughout the duration of the Joint Action. In addition, some further alternatives were provided for consideration.

**OBJECTIVE 1: Strengthening use, usefulness and suitability of registries for HTA-based patient and consumer safety and monitoring**

The target of the HTA-oriented objective is to make patient registries a reliable, accessible and usable source of real world data on the basis of which information can be derived on relative efficacy as well as on short- and long-term effectiveness, when applicable, of health technologies (medicinal products & devices). In the case of medicinal products, recent EU legislation recognizes post-authorization
safety and efficacy studies (PASS, PAES), while the reform of the Medical Devices Directive aims at promoting better traceability of devices throughout the supply chain and places clear emphasis on ensuring patient and consumer safety. The underlying objective is support to the efforts of ensuring sustainability of health systems’ services.

Proposed HTA-related actions

- Develop a shared understanding and guidance regarding definition and purpose of use of various registry types, to be reflected in methodological guidance of both patient registry and HTA initiatives.
- Increase availability of HTA-meaningful data & publications
  - Establish time-critical processes for HTA-needed registry data acquisition
  - Establish a process of notification of registries with regard to emerging/new technologies.

OBJECTIVE 2: Supporting ERNs and rare disease services & research

The Cross-border healthcare directive clearly indicated the role of registries in support of European Reference Networks’ objectives: “…to reinforce research, epidemiological surveillance like registries and provide training for health professionals”. Since the Directive also indicates as one of the most suitable areas for ERNs that of rare diseases, it can be assumed that rare disease registries could also be an area of focus.

We have identified two distinct opportunities in the cycle of ERNs development for bringing forward the results achieved by PARENT: the Technical Assessment process of networks applying for ERN status (criteria and conditions) and the Evaluation process (criteria, performance and cooperation) of established ERNs.

In addition, we have identified several targets set by the Directive to the operation of ERNs, whereby registries could act as the tools and means for achieving the respective goals:

- Improvements in diagnosis and delivery of high-quality, accessible and cost-effective healthcare
- Gaining evidence of good outcomes
- Implementing outcome measures and quality controls

Proposed actions: Reflection of registry best-practices in the formulation of the technical assessment and evaluation criteria for ERNs and in the actions included in national plans for rare diseases.

Objective 3: Increasing interoperability & comparability of patient registries

Interoperability in its various aspects has been a central element in the work of PARENT Joint Action, as reflected for example in the areas of minimum data sets and the identification of medicinal products and devices. At the same time, interoperability presents a major challenge for PARENT since it is a domain where a balance has to be sought between national competencies vs. the areas where EC/EU level action is needed.
The status of progress with regard to healthcare ICT implementation (eHealth) is still variable across Member States, but any possibility to truly advance towards interoperable, IT-enabled registries relies on the implementation of a national infrastructure featuring the elements necessary for eRegistries to operate.

PARENT work on MS health data strategies has revealed several areas of convergence:

- Similar type registries established (in terms of content focus) as the basis of national health information systems
- Strategic aim of connecting EHR data and registries
- Research as a theme and as an economic driver for public health cost savings and enterprise development opportunities
- Links to biomedicine and biopanking

In parallel to the activities of PARENT, there are also wider ongoing initiatives having possible synergies with and impact on health data/registry work. These include, among others:

- eGovernment
- INSPIRE and spatial data
- Open data initiatives/eScience
- Biomedicine projects

**Proposed actions:**

- Ensure health data viewpoint representation in parallel activities of high priority and promote patient registry-specific needs
- Placement of secondary use of data and patient registries on the national ehealth strategy roadmaps
- Establishment of registries (PARENT) NCPs – taking into account the Directive mandated NCPs and currently active epSOS NCPs.

**OTHER POTENTIAL USES OF PATIENT REGISTRIES**

As indicated in Article 4 of the Directive (under healthcare providers’ responsibility) and confirmed in the Health Programme thematic priority 4, a central objective is to “...increase the availability of information to patients on safety and quality, improve feedback and interaction between health providers and patients.”

A concrete step in promoting the achievement of this goal would be the inclusion of patient-relevant outcomes (incl. PROM) in registries’ data collection & reporting planning and practices.
Group work questions and feedback
After presenting these draft proposals to Seminar participants, work continued in the form of three break-out sessions, where each group discussed and provided feedback to the plenary on the basis of the following questions:

- What is your understanding of the policy objectives presented in EU documentation?
- What are the means for achieving them?
- Which of the means seem more realistic and what obstacles to progress can be identified (e.g. gaps in regulatory framework)?

Each group was assigned two rapporteurs of the WP6 team, who then provided an overview of the topics and ideas discussed during the group work. A summation of the feedback we received is presented below.

HTA-related activities
Participants acknowledged that this is a collaborative European effort where registries could be utilized. Interoperability issues (in particular semantics) as well as legislation are critical in that respect. At the moment delays in providing data are too long. Utilization of registries is not expected to eliminate the need for clinical trials, e.g. when new devices are introduced. Different practices in use of data between the national and international use of data, particularly with regard to subject’s consent.

ERN-related activities
The importance and relevance of the topic was acknowledged, however the concern was raised that it is not realistic to aim for an all-encompassing set of criteria for registries. Very distinct and different targets and practices between rare disease registries and registries which cover major pathologies. In the latter, comprehensiveness of population coverage is the strength and the challenge focuses in the recognition of non-identified/non-diagnosed patients. Limited pathologies on the other hand have very specific needs with regard to criteria and their main challenge is the identification of patients. The central role of the legal and regulatory framework was a recurring theme. Legal instruments are an essential tool in utilization of patient registry data. At the same time laws and regulations may act as an obstacle, when they do not not provide for the flexibility and timelines often needed in registry based research.

The concept of NCPs for registries was considered an interesting proposal. It needs to be elaborated and specified further as part of the overall analysis of the PARENT framework and the ongoing preparation of proposals for action.

Stakeholders: Seminar participants were still expecting a clearer message from PARENT, which then could be brought further by requesting the support of the eHealth Network.

National stakeholders were viewed as a bigger challenge than international ones; they do, however, have a central role in ensuring quality of data in registries. Showcase examples are needed for people and systems to learn from best practices. Registries should be profiled as an essential component of sustainable health information systems and their requirements.
Annex 2 – Note to Commission Expert Group on Rare Diseases

NOTE
From: EXPAND, the EUCERD Joint Action for RDs, the PARENT Joint Action for Registries, and EURORDIS
To: EC Expert Group on Rare Diseases
Subject: eHealth Strategies and Roadmaps supporting European Reference Networks and rare disease policies
Submitted: June 1st, 2015

I. INTRODUCTION

1. Directive 2011/24/EU promotes policy co-ordination and MS co-operation through the eHealth Network, established through its Article 14. In May 2014 the eHealth Network adopted four priorities for eHealth two of which – namely the cross border Patient Summary and ePrescription services have been included in the 2015 work programme of the CEF (the Connecting Europe Facility2), while the potential inclusion of services supporting European Reference Networks and Registries has been postponed to a later point in time. On the other hand, the implementation of Patient Summary and ePrescription services, included in the 2015 CEF work program, constitute the initial set of CEF supported eHealth services and is expected to put in place the basic infrastructure, governance and interoperability framework needed to enable the exchange of health data based on a clear legal basis, and within a secure and trusted environment. These are important enablers that set the foundations for rapid expansion to new health data sharing services, addressing health care challenges beyond emergency care services and especially the priority areas of Directive 2011/24/EU such as for European Reference Networks (ERNs) which has evolved a set of information exchange expectations that need to be met.3

2. The European eHealth Strategy and Roadmap as expressed through the EC Recommendation on cross-border interoperability of electronic health record systems,4 the CALLIOPE Roadmap5 and the eHealth Network guidelines for Patient Summaries and ePrescriptions, have focused initially on addressing fundamental challenges of interoperability of electronic patient records exemplified through patient summary and ePrescription services; re-using this data for acquiring new knowledge for the

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2 The Connecting Europe Facility (CEF) finances projects which fill the missing links in Europe’s energy, transport and digital backbone. Improving digital service infrastructures is a major part of the Connecting Europe Facility. "CEF Digital" (http://ec.europa.eu/digital-agenda/en/connecting-europe-facility) has a budget of 1.14 billion euros, out of which 970 million euros are dedicated to Digital Service Infrastructures (DSIs).

3 Commission delegated decision (http://ec.europa.eu/health/ern/docs/ern_delegateddecision_20140310_en.pdf) listing the criteria and conditions that healthcare providers and the ERNs should fulfil; Commission implementing decision (http://ec.europa.eu/health/ern/docs/ern_implementingdecision_20140310_en.pdf) containing criteria for establishing and evaluating ERNs, including the exchange and dissemination of information about the ERNs

4 COM(2008)3282 final

improvement of care and care processes is a natural next step. This is reflected in the prioritization of the eHealth Network concerning the European Digital Service Infrastructure (DSI) to be developed under CEF. A similar trend is observed at national and regional level.

3. Strategies for addressing rare disease (RD) challenges at EU and national level exist, as RD are considered a priority area for action at the European level in view of the potential for European added-value through a collaborative approach. This commitment to RD has been enshrined in a series of key policy documents and is evident in the constitution of entities such as the RD Task Force, the EU Committee of Experts on RD (EUCERD) and, most recently, the Commission Expert Group on Rare Diseases (CEGRD). The EUCERD and CEGRD have issued Recommendations on topics of particular relevance to RD, to support Member States in addressing the challenges posed by RD. To date, Recommendations have been adopted for: RD European Reference Networks; RD Patient Registration and Data Collection; the CAVOMP-Information Flow; Quality Criteria for Centres of Expertise for RD; Core Indicators for RD National Plans; Ways to Improve Codification for Rare Diseases in Health Information Systems. These policies aim to support Member States in elaborating and implementing national plans/national strategies for RD (which the EC had recommended MS adopt before the end of 2013, to guide and structure relevant RD activities within the health and social frameworks).

4. These two policy areas (rare disease and e-Health) have been addressed separately and largely without coordination to-date. The e-Health efforts in the Registry community, for example, start from the point where data and information has already been gathered at individual RD centres and needs to be shared to support patient care and research. The discussion on how has this data/information been collected, by which means, tools, systems and in what format has only recently been considered.

5. Action at all levels and a long-term strategy for convergence of efforts are urgently needed, which should aim at proactively addressing Rare Disease, Registries and European Reference Networks needs within European and national/regional level eHealth strategies. Likewise, eHealth specific considerations should become part of national strategies and action plans for Rare Diseases.

6. These proposals are being developed and justified within the Exploratory paper, titled “eHealth Strategies and Roadmaps supporting European reference Networks and rare disease policies”, produced by an informal joint group of experts from the four initiatives within the work and mandates of the EXPAND Thematic Network, the EUCERD and the PARENT Joint Actions on Rare Diseases, and EURORDIS. The paper explores how ERN and EU Registry needs may be addressed in CEF, as extensions of eHealth DSIs.

II. PRIORITIES FOR THE EHEALTH NETWORK AND RARE DISEASE COMMUNITIES

6 E.g. Commission Communication on Rare Diseases: Europe’s Challenges, COM (2009) 679; Council Recommendation on an action in the field of rare diseases (2009/C 151/02; Directive 2011/24/EU; Regulation (EC) 141/2000 on Orphan Medicinal Products (OMPs); Regulation EC 847/2000 on OMPs; and Commission Communication on OMP 2003/C178/02
8 PARENT Joint Action has systematically worked to promote awareness and actions supporting the continuum of health data from the point of patient care and services provision, to publish health and other patient data repositories.
9 EXPAND (2014-2015) is an eHealth thematic network supported by CIP, building upon the achievements of previous projects, notably epSOS to ensure sustainable, scaled-up, pan European investments in the field of eHealth.
10 The EUCERD Joint Action: Working for Rare Diseases is a healthcare policy project which supports the European Commission (EC) in formulating and implementing healthcare policies pertaining to rare diseases (RD) across Europe, in order to reduce inequalities in access to quality RD healthcare. It worked closely with the EUCERD (and now the Commission Expert Group on Rare Diseases). The policy priorities of the EJA will continue under the new JA for RD, RD-Action, due to begin summer/Autumn 2015.
7. Healthcare and research are very much interlinked in the RD field; digital platforms, such as the platform of RD-Connect aim to allow clinicians and researchers across Europe to share de-identified genomic and phenotypic data with other professionals, which will support diagnosis and clinical practice as well as research.

8. Data sharing is a major priority in the RD community. Sources of data for RD patients are scarce and, at present, largely fragmented. A priority for any eHealth service should be to enable the integration of (possibly-disparate) sources of data: this might be data from registries, from EHRs, from biobanks etc.

9. For this to become possible, unambiguous electronic identification of patients, across countries and across databases is key. Appropriate anonymisation services are also necessary to allow for anonymisation of information for research. It is also becoming increasingly accepted that certain critical information for rare disease patients is necessary in order to follow them throughout the healthcare pathways (e.g. Rare Disease cards).

10. Ongoing work around European Reference Networks and the services that they should provide has clearly shown that interoperability between centres of expertise (or healthcare providers as per Dir 2011/24/EU) is recognised as the greatest obstacle that needs to be overcome for full deployment of ERNs. Hence, establishing common semantic and technical standards is a priority for the RD community, which is directly and intrinsically concerned with ERNs and their already mentioned information needs which have been preliminarily outlined.

11. It is necessary that RD are adequately integrated both to ‘planned’ care (or shared expertise and/or care) systems via ERNs, and also to systems dealing with emergency and unplanned care. Given the specificities of RD, it is important that tools to facilitate cross-border care (such as ePrescription and Patient summaries) can adequately convey core information on rare conditions and treatments (e.g. are coded appropriately). There has been little emphasis on this, to date.

12. Key to the cross-border interoperability of data in the RD field is the use of appropriate ontologies. It is recognised that RD are typically far less ‘visible’ in health information systems compared to more common diseases, as the major systems of disease classification (e.g. ICD10) are at present unable to capture the complexities and granularity of RD. Developing and promoting use of a shared -and RD appropriate- coding nomenclature is thus a key priority for the field. The Orphanet rare disease ontology (ORDO) is considered to be the most appropriate “nomenclature” system for RD.

13. ICT tools supporting shared care in the area of RD, notably EHRs, should also enable clinical (phenotypic) information to be collected in a computable way, thus enabling the identification and centralisation of information about patients with specific conditions across centres of care, whether Centres of Expertise, local clinics, hospital emergency departments etc. For RD

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11 See also PARENT Study “Patient Registries as Tools in support of the Cross-border Healthcare Directive”.

12 ICD10 is able to code only ca. 250 of 6-8000 RD

13 “Ontologies utilized by RD research projects should build upon existing best practice and allow integration and interoperability across different ontologies, including those for model organisms. Ontologies should include a RD classification ontology (nosology), a phenotype ontology with comprehensive coverage of RD manifestations including laboratory values and imaging, as well as ontologies to support biobanking, clinical trials, and research”. (IRDiRC policies and guidelines).
patients, due to their dispersal across different health care systems, this need is even more important. Collecting an adequate threshold of such phenotypic information allows for health improvement, improved research and more empowered patients.

14. Further health potential lies in the exchange of data stemming from improved genome screening techniques and better bioinformatics tools to interpret genome/phenome data. Data-sharing should always be supported by an adequate ethical/legal/social framework that corresponds not only to ethical standards and legal requirements, but also to patient preferences.

III. BEYOND CROSS BORDER PATIENT SUMMARY AND ePRESCRIPTION SERVICES

15. The current European patient summary for unscheduled care, provided in a different European country from the patient’s usual place of care/place of residence,

- contains generic information that will not be particularly helpful for people seeking to provide continuity of care to patients with rare diseases, nor contain the data items that are most needed to select patients that are relevant to a rare disease related study;
- contributes to increased safety in unplanned care situations but less so to continuity of care through e.g. updating of medical records in the patient’s country of affiliation; it is however noted that this concept has been implemented in epSOS\textsuperscript{14} in the return of the dispensation report (the eDispensation document) in the ePrescription services and in the “Health Care Encounter Report” (HCER, summarising results of an encounter in the country of treatment, when a Patient Summary was retrieved from the country of affiliation);
- enables the exchange of codified data elements in electronic clinical documents but does not support the exchange of imaging data;
- makes available to the treating physician in the country of treatment information from a single source i.e. the NCPeH (National Contact Points for eHealth\textsuperscript{15}) of the country of affiliation while shared care requirements through ERNs may require longitudinal care views from multiple sources (members of the ERN);
- does not include in its current services tele-consultation components.

16. The first set of eHealth services to be deployed in CEF will exploit a number of use case-specific semantic and technical interoperability assets developed and validated within the epSOS Large Scale Pilot with extensions especially for eID and non-repudiation developed and expected to be piloted under eSENS\textsuperscript{16} these are already on the eHealth deployment agenda. There is in addition also a wealth of existing and forthcoming interoperability assets from the RD field with potential to support relevant use cases in CEF, such as the RD-Connect Global Unique Identifier (GUID); the Orphanet Rare Disease Ontology (ORDO); the RD-specific Human Phenotype Ontology (HPO) terms; a number of searchable databases; Minimum Datasets; catalogues of general\textsuperscript{17} and RD-specific resources (biobanks and registries)\textsuperscript{18} that contain details of what the resource holds;

\textsuperscript{14} epSOS (www.epSOS.eu), an EC-co-funded project that ended in 2014, aimed to design, build and evaluate a service infrastructure that demonstrates cross-border interoperability between electronic health record systems in Europe.
\textsuperscript{15} eHealth NCPs are distinct entities from those established under Directive 2011/24/EU.
\textsuperscript{16} e-SENS (Electronic Simple European Networked Services, www.esens.eu) is a new large-scale project that embodies the idea of European Digital Market development through innovative ICT solutions.
\textsuperscript{17} PARENT Registry of Registries (RoR), http://www.parent-ror.eu/about/
guidelines promoting interoperability and quality of registries\textsuperscript{19} and codes of practice, to mention but a few.

17. It is important to note that many of these assets are currently developed and maintained within projects; their sustainability and systematic maintainance will need to be secured.

18. On the basis of the above, it is sensible to assume that extensions of cross border eHealth DSIs will need to demonstrate that

- there is a clear policy priority under Directive 2011/24/EU;
- there exists an infrastructural need at a European level that addresses an important integration gap and will deliver real added value to the implementation of this policy if it is met;
- this integration functionality will not be provided through the services that the CEF already plans to deliver, and
- the additional interoperability services can draw on mature specifications and standards that have consensus acceptance within the user community.

IV. A USE CASE BASED APPROACH, EXTENDING eHEALTH DSIs

19. The following few examples are used to demonstrate how possible use cases addressing ERNs and Registry specificities in the light of the eHealth Network CEF priorities, may be prioritized as extensions of the patient summary and ePrescription services foreseen for deployment in CEF, as of 2016. The intention is to exemplify how, well defined, needs may be addressed though leveraging on a foundation of eHealth DSIs and interoperability assets developed by several communities.

a. RD specificities in the European Patient Summary may be envisaged as an extension of the current data set to include data elements necessary for identifying RD patients and for adequately conveying core information on rare conditions and treatments. This would leverage available RD assets such as the ORDO and links to resources that would help physicians deal with a rare disease encounter.

b. Supporting planned care through shared care records may be envisaged as an evolution of the Patient Summary service to address the needs of planned care, starting from selected diseases. This may be implemented through the Health Care Encounter Report service, extended with the same proposed Patient Summary datasets for RD, which will allow the return of information for incorporation into the patient’s health care record.

c. Exchanging Health Care Encounter Reports (HCER) i.e., standardized data sets of information generated as a result of a health care encounter and that needs to be shared within other health professionals sharing responsibility for the care of a patient may support ERN needs and sets the foundations for services supporting Registries by linking EHRs to Registries.

\textsuperscript{19} PARENT Methodological Guidelines and recommendations for efficient and rational governance of cross-border patient registries.

\textsuperscript{20} these will not be supported under CEF 2015; although the HCER service was analysed in epSOS only segments were developed in epSOS and Trillium Bridge\textsuperscript{20} for demonstration purposes;
agreed clinical data sets exist for a number of rare diseases, while there is a substantially comprehensive shared data set across different clinical areas;

- there are mature specifications and standards some of which are under consideration for adoption by the Multistakeholder Platform (MSP).

d. Extending eID services provided for Patient Summary and ePrescription needs, to include the Global Unique Identifier for patients/research participants which could allow clinicians and researchers to 'link' genome sequencing data with essential phenotypic information gathered in shared care EHRs.

20. The above examples, can also help illustrate the kind of additional work which will be needed to implement, test and validate extensions beyond the existing demonstrators, prepare the available semantic assets which might need additional processing, e.g. where appropriate to convert it in the form of a respective Master Value Catalogue21, for deployment in CEF and validate the service within a small scale pilot involving a number of centers and countries, members of the respective ERNs.

21. A prioritization exercise should also examine gaps that need to be addressed before launching new services on CEF. For example, the epSOS specifications of HCER will need to be tailored to the planned care shared record 22; this will require introducing extensions to the Patient Summary use case, elaborate specifications, testing, deployment governance and related policies, hence it is unlikely that it could be addressed as such it in CEF 2016 and additional work will be needed before deployment. Additional work will be also needed to perform a legal and organizational gap analysis, implement, test and validate these additional services within the small scale pilot involving a number of centers and countries, members of the respective ERNs to assess the organizational, technical and cost implications of accessing data in shared care electronic records; following this to implement possible additional profiles and respective technical extensions, test and validate these additional services within the small scale pilot involving a number of centers and countries, members of the respective ERNs.

V. NEXT STEPS –PROPOSED ACTION

22. The current, project based, expert group and its activity should be commissioned as a “Convergence” Task Force that will be tasked to elaborate proposals to the eHealth Network subgroup for implementation of eHealth DSIs (SG4i), and the European Commission regarding:

- a stepwise, use case based implementation approach and a strategic roadmap of activities supporting convergence between the eHealth domain and the relevant RD, ERN and Registry related activities;

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20 Trillium Bridge (http://www.trilliumbridge.eu/), co-funded by the European Commission, is a project aimed to establish the foundations of an interoperability bridge to meaningfully exchange patient summaries and electronic health records among the EU and US.

21 The Master Value Sets Catalogue is a collection of terms used within certain parts of the epSOS pivot documents (either parts describing the patient demographics or the clinical problems, for example) based on standardized code systems such as ICD-10, SNOMED CT, ATC, EDQM and UCUM.

22 The following 3 links to OpenNCP Community materials display mature specification for the use cases, in the context of the OpenNCP:

HCER: https://openncp.atlassian.net/wiki/display/ODC/HCER+Service+for+Patient+Summary+Extension
MRO: https://openncp.atlassian.net/wiki/display/ODC/Medication+Related+Overview
PAC: https://openncp.atlassian.net/wiki/display/ODC/Patient+Access+to+Information+PAC
• what actions need to be launched immediately in order to support a possible extension of CEF eHealth DSIs within the CEF 2016 work plan; such extensions should represent use cases addressing eHealth Network priorities, which are also priorities of the rare disease community to be implemented through ERNs and other means within the scope of Directive 2011.24/EU;

• the strategic elements that need to be incorporated into EU and national and regional strategies for eHealth and for Rare diseases.

23. The Task Force should also provide support to the European Commission and the eHealth Network subgroup for implementation of eHealth DSIs (SG4i):

• to identify immediate extensions meeting the criteria for CEF for eHealth services to be included in the CEF 2016 programme, and

• to agree the respective immediate activities beyond the scope of the work of EXPAND and the current Joint Actions (for Rare Diseases, Registries and eHealth) that are needed to prepare the assets for these extensions including a unified conformant approach.

24. The currently running initiatives – projects and existing and new Joint Actions - have supported and are expected to continue to support a certain level of co-operation and activities such as joint workshops, to discuss and validate the Exploratory document; however none of the existing projects has a mandate to prepare assets for extended services for CEF. If eHealth extensions will be included in the CEF 2016 work programme, **a supplementary activity to this end will become urgent.**

25. On the other hand, a number of projects are selecting and adopting use cases suitable to help them carry out their work objectives. **There is an urgent need for an activity that would reflect on and deliver a proposal for a Roadmap of use cases and associated work elements** necessary to address in a stepwise and prioritized approach the full span of cross border eHealth needs implicit in the Directive. This Roadmap could become a valuable policy support instrument in terms of setting common implementation priorities.
Annex 3. Literature Review on cross-border registries

The literature review undertaken by WP6 had the purpose of providing us with background information on the current situation of cross-border/international registry data use as reflected in peer reviewed publications, and on the other hand to map the extent that eHealth solutions (in particular EHRs and the data they contain) have been utilized in this context. Respectively, the work of the literature review (database searches, review of abstracts and full-text materials, analysis of results etc.) was divided into two thematic strands. The theme of EHR data utilization did not return adequately relevant material. Hence we report here primarily on the analysis of materials retrieved on the subject of cross-border use of registry data.

Methodology

For both strand themes the following databases were searched: Medline (OVID), PubMed, Academic Search Elite (ASE), Web of Science, ProQuest Health Management. Search terms were defined according to the terminology applied by each database and supplemented with text search. The searches were conducted and duplicates removed at the end of June 2012 by a professional informatician (librarian). Tables 1 and 2 show for each theme the databases searched, the number of references found in each database and those remaining after removal of duplicates. In total 258 unique references were identified for the first theme (registries), and 134 for the second (medical records).

Table 1. Overview of databases used and references located on the subject of cross-border use of registries

<table>
<thead>
<tr>
<th>Database</th>
<th>Number of reference after removal of duplicates</th>
<th>New references from the specific database</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medline (177)</td>
<td>174</td>
<td></td>
</tr>
<tr>
<td>Web of Science (63)</td>
<td>227</td>
<td>53</td>
</tr>
<tr>
<td>ProQuest (22)</td>
<td>242</td>
<td>15</td>
</tr>
<tr>
<td>PubMed (20)</td>
<td>244</td>
<td>2</td>
</tr>
<tr>
<td>ASE (14)</td>
<td>258</td>
<td>14</td>
</tr>
</tbody>
</table>

Table 2. Overview of databases used and references located on the subject of cross-border use of medical records

<table>
<thead>
<tr>
<th>Database</th>
<th>Number of reference after removal of duplicates</th>
<th>New references from the specific database</th>
</tr>
</thead>
<tbody>
<tr>
<td>PubMed (55)</td>
<td>55</td>
<td></td>
</tr>
<tr>
<td>Medline (34)</td>
<td>77</td>
<td>22</td>
</tr>
<tr>
<td>Web of Science (24)</td>
<td>101</td>
<td>24</td>
</tr>
<tr>
<td>ProQuest (20)</td>
<td>118</td>
<td>17</td>
</tr>
<tr>
<td>ASE (16)</td>
<td>134</td>
<td>16</td>
</tr>
</tbody>
</table>

Review of the references at the level of abstracts was performed by two members of the team, based on the following inclusion criteria (adjusted accordingly for the each thematic strand):
• Article in English language
• Publication concerns linking of data residing in at least two different countries/registries
• Purpose of linkage is explained
• Opinion papers (only when addressing the subject of interest)

Articles were excluded when: they were written in a language other than English, concerned news, clinical trials (we just recorded how often such publications were encountered), or focused on low and low-middle income countries.

The first thematic strand of the literature review has the aim of providing answers to the following questions:

1. What experiences can be identified in the literature regarding cross-border use of register data?
2. What was the purpose of data linkage?
3. What are the (clinical) areas of focus – types of questions that cross-border data use has aimed to answer?
4. How large were the data samples used?
5. Which countries were involved?
6. Identified successes and outputs of relevant efforts
8. Business models, sustainability needs, governance models – possibly e-Infrastructure (if mentioned): noted, to be analysed as part of subsequent work

Results
After review and application of the exclusion criteria at the abstract level (Strand 1 – cross-border use of registries) we had the following situation:

129 articles = Included for further analysis
33 = Uncertain (publications potentially useful as background materials, final inclusion decision to be made after full-text review)
78 = Excluded (of which 18 concerned clinical trials).

The distribution of the included 78 publications per clinical area is presented in Figure 2.

Correspondingly, the initial analysis of abstracts for Strand 2 on cross-border use of medical records resulted in the following situation:

24 articles = included for further analysis
158 articles = excluded (part potentially useful as background materials for policy analysis).

The profile of the publications identified through the Strand 2 searches appeared to concentrate around two themes: record linkage for clinical studies and issues pertinent to EHR networks and interoperability (semantics, standards etc.). As we proceeded with the full text review of included abstracts we concluded that there was limited added value to be achieved from analysis of the material and hence stopped the process.

The remaining text in this section focuses in a more detailed presentation of the findings of the Strand 1 literature review on cross-border registries. Findings are presented in the format of standardized “info pages” (to the extent possible, since there were differences between the material pertaining to specific clinical areas). It is to be noted that the literature search results were of variable quality; for most articles there was a full abstract available, but for some there was only the reference to the article’s title.
The main purpose of the ‘info pages’ is to give an overview of each clinical area covered in the literature; the purposes and points of the articles by topic, division by subtopic, study purposes etc., thus forming the basis for the more detailed phase of the literature review. In order to point out articles requiring in-depth examination, references concerning studies with presumed record linkage across registries, potential studies on patient safety and potential studies linking drug use and health status are counted and listed separately.

For international registries and registry networks, the information was complemented in some cases with internet searches, in order to find information about their geographical coverage and patient populations. Detailed cases are recorded and grouped in view of further analysis. In addition to the written description of each topic, most “info pages” are also accompanied by a graph which points out the national and international registries which could be detected, and the connections between them. These graphs are neither fully accurate nor complete, since all information cannot be expected to be found in the abstracts and/or references, but they are meant to give an approximate idea of the geographical focus and strongholds of the research on each topic.

A total of 40 unique registries with international activity have been identified through our review until now (see Table in Annex 1).

![Figure 2: Distribution of included articles per clinical area (theme 1 – cross-border registries)](image-url)
Topic “Cardiovascular conditions”

37 articles – 2001-2010, Grouping based on study/registry:

**GRACE (Global Registry of Acute Coronary Events) Study (Project)** (11 references):
“a large, prospective, multinational observational study of patients hospitalized with Acute Coronary Syndrome (ACS). The aim of GRACE is to improve the quality of care for patients with ACS by describing differences in, and relationships between, patient characteristics, treatment practices, and in-hospital and post-discharge outcomes at hospitals around the world. A goal of this study is to study approximately 10,000 patients with ACS on an annual basis.” (21)

The aim of GRACE was to provide a large multinational registry of the full spectrum of patients with acute coronary syndromes (ACS) in order to define patient characteristics and outcomes and derive predictive risk scores. The study was designed and administered by an independent steering committee; data analyses were performed under the guidance of the steering committee at the Center for Outcomes Research of the University of Massachusetts. Regular feedback regarding local, regional and international guideline and performance measures was provided to individual hospitals and clusters of hospitals. Regional and international benchmark data were available to all sites. Main GRACE involved 123 hospitals in 14 countries in North and South America, Europe, Australia and New Zealand. **GRACE2 (Expanded GRACE) comprised 154 hospitals in Europe, North and South America, Asia, Australasia and China.** Continuous recruitment and follow-up took place between 1999 and 2009. The first 10 -20 patients per site (depending on hospital size) were enrolled each month, resulting in the **recruitment of 102 341 patients**, who were categorized as having ST-segment elevation myocardial infarction, non-ST-elevation myocardial infarction or unstable angina. According to information available on the GRACE web site ([http://www.outcomes.umassmed.org/GRACE/interactive/methodology/datasubmission.htm](http://www.outcomes.umassmed.org/GRACE/interactive/methodology/datasubmission.htm)), standardized case report forms (datafax or electronic) were completed by trained study coordinators, and included fields relating to demographic factors, comorbid conditions, treatments and in-hospital and post-discharge (6-month) events and transmitted between participating hospitals and Premier Research (a division of SCP Communications in Philadelphia, USA responsible for all data management activities in GRACE) using the DataFax™ system. Blood sampling, genetic analyses and longer-term follow-up were undertaken in GRACE sub-studies. Prospective individual patient follow-up was carried out. **All sites were audited locally; 10% of individual patient records were audited in a 2-year cycle.** Less than 1% of 20 key baseline fields, and less than 1% of discharge diagnosis and discharge status data were missing. Six-month follow-up was 85% complete. Publications and risk scores are available at [http://www.outcome.org/grace](http://www.outcome.org/grace). Proposals for specific analyses were considered, in competition, by an independent publications committee.

Study purposes: equipment/procedures (4), medications (3-5), epidemiology (3) predictive risk scores, patient outcomes (during and post-hospitalization), management practices.

**BASICS (Basilar Artery International Cooperation Study)** – rare cause of stroke) – 2 references: Prospective, observational, multi-center, international registry of consecutive patients presenting with a symptomatic and radiologically confirmed basilar artery occlusion. Main purpose of the registry is to collect preliminary data that will help direct the design of a future clinical treatment trial. 42 centers in 12 countries. The target number of patients included was 500 - Findings of 619 patients were entered in the registry. Data collection from 2002 to 2007.

Study purposes: equipment/procedures, medications

The **Benchmark Counterpulsation Outcomes Registry** – 1 reference, no detailed information. Large multinational Intracoronary balloon counterpulsation (IABP) data registry. Focus: Procedure - patient
outcomes. Comparison between international registry and Australian cardiothoracic tertiary referral hospital.

**International Cooperative Pulmonary Embolism Registry (5 references - #75, 235, 90, 91, 152)**
Pulmonary embolism (PE) remains poorly understood. Rates of clinical outcomes such as death and recurrence vary widely among trials. We therefore established the International Cooperative Pulmonary Embolism Registry (ICOPER), with the aim of identifying factors associated with death. 2454 consecutive eligible patients with acute PE were registered from 52 hospitals in seven countries in Europe and North America (1995-1996?). The primary outcome measure was all-cause mortality at 3 months. Data from ICOPER provide rates and highlight adverse prognostic categories that will help in planning of future trials of high-risk PE patients.


There are currently **nine different datasets used throughout the world** to collect patient information. To harmonize the considerable diversity among these source materials, an **International Dataset has been developed** by a collaborative process among more than 50 cardiac surgeons around the world. Constructed around the **Society of Thoracic Surgeons (STS) data format**, the International Dataset brings in key elements from all the other datasets, allowing the sharing of data and cross-analysis, thus greatly expanding the pool of patients, and national sources, from which risk-stratified outcomes can now be analyzed and unified. Unlike the STS dataset, the International Dataset **incorporates EuroSCORE**, a simple-to-use, validated patient risk stratification system, which has been rapidly adopted by large numbers of centers around the world for patient risk stratification, outcomes assessment, and improving patient informed consent. There are several **benefits to collecting and centralizing national and international data**: (1) understanding and defining basic demographics of patients undergoing cardiac surgery; (2) patient risk stratification and risk prediction at both a national and center-by-center level; (3) unit bench-marking, and development of effective nationally oriented and center-oriented quality improvement programs; (4) understanding and rationalizing resource utilization; and (5) use of data to leverage governments and other healthcare providers to affect policy. Cardiac surgical registries will soon attempt to track patients for longer follow-up periods after discharge in order to identify surgery-related deaths for more extended periods of time following surgery, thereby improving the monitoring and prediction of patient outcomes.
**Topic “Cancer”**

18 articles; 1976 - 2011.

Grouping based on article purpose/point: Study (12), Study combining 2 registries’ data (1), Registry (1), Registry network (1), Study on international coordination of efforts (1), Study Proposal (1), Programme (1), Discussion (1).

Subtopics’ count where feasible:
Cancer in general (4), Cancer survival (3), Cancer in children (1), Colorectal cancer (1), Breast cancer (1), 2nd malignancies following testicular & ovarian cancer and Hodgkin’s disease (1), Cancer in patients in dialysis for end-stage renal disease (1), 2nd primary cancers in thyroid cancer patients (1), Families at high risk of pancreatic cancer (1), Tonsil cancer; incidence & survival (1), Hereditary nonpolyposis colorectal cancer (1).

Study purposes where feasible:
Determining prevalence and comparing demographics of cancers, Registration / case ascertainment quality, Registration and its uses in research and confidentiality in the EC (#220). Investigating survival disparities with the aim of informing health policy to raise standards and reduce inequalities in survival. Evaluating the effectiveness and safety of SEMSs as an alternative to emergency surgery. Risk factors’ assessment. Screening of risks of familial cancers. All articles for which full abstracts were available were about combining national registries’ data; no international registries or registry networks were detected.

Articles on studies with possible record linkage across registries: 10
Of these: potential studies on patient safety: 4
Of these: potential studies linking drug use & health status: 0

Collaboration/linkage between countries/registries (based on information available in abstracts):
Topic “Stem Cell Donation & Transplantation”

13 articles; 1988 - 2010.

Grouping based on article purpose/point:
Registry Network (11), Registry (1), Unclassified (1)

Subtopics’ count where feasible:
Bone Marrow (9), Human Embryonic Stem Cells (1), Cord Blood (2), Stem Cells/Cord Blood (1).

Study purposes where feasible:
Stem Cell Donation and Transplantation, including bone marrow, cord blood and other sources, seems to be covered by registry networks very well on a global scale. Most articles are about these networks and their functions; registering of donors, collecting and sharing samples, and guidelines. Also research is being made to further enhance the functionality of the networks, by e.g. cutting off overlaps. There were no articles describing record linkage of particular registries; almost all cooperation seems to be coordinated by the international networks.

Articles on studies with possible record linkage across registries: 0
Of these: potential studies on patient safety: 0
Of these: potential studies linking drug use & health status: 0

Collaboration/linkage between countries/registries (based on information available in abstracts):
**Topic “Organ Donation & Transplantation”**

13 articles; 1988 - 2012.

Grouping based on article purpose/point:
Registry (11), Study (2)

Subtopics’ count where feasible: Small bowel transplantation (1), Pancreas transplantation (1), Donors and donations; volumes and trends (1), Transplant tourism: removals from the waiting list for procedure abroad (1), unclassified (9)

Study purposes where feasible:
7 of the articles are regular reports of the Registry of the **International Society for Heart and Lung Transplantation (ISHLT)**, and for none of them a full abstract is available. Two are reports of the **ISHLT Mechanical Assisted Circulatory Support Registry**, also no abstracts. Other international registries detected include the **International Online Registry for Organ Donation and Transplantation (IRODaT)**, which does regular reporting on global trends, e.g. to make organ donation effectiveness rates a useful tool to reveal similarities between various countries on an international level. The **Intestinal Transplant Registry** tracks down world experience reviewed since 1985 to determine the current status of small bowel transplantation. The **United Network for Organ Sharing (UNOS)** and the **International Pancreas Transplant Registry (IPTR)** have done analysis on pancreas transplantation cases since 1987. The **US National Transplant Waiting List** has been studied to determine the scope of “transplant tourism” by searching removals from the US waiting list for procedure abroad.

Articles on studies with possible record linkage across registries: 1
Of these: potential studies on patient safety: 0
Of these: potential studies linking drug use & health status: 0

Collaboration/linkage between countries/registries (based on what is clear from abstracts):
**Topic “Orthopaedics / Arthroplasty”**

10 articles; 2008 - 2012.

Grouping based on article purpose/point:
Study (4), Registry (3), Registry Network (3)

Subtopics’ count where feasible: Venous thromboembolism after total arthroplasty (1), Dura lesions in posterior spinal fusion (1), Prosthesis survival (1)

Study purposes where feasible: 6 of the articles are about international arthroplasty/orthopaedics registries. 2 are about studies linking national registries’ records. Subtopics in Registry/Registry network type articles covered e.g. supporting founding of national registries, development of universal prosthesis classification systems, and differences among countries concerning patient demographics. The study type articles were about comparison of demographics, choice of implants, techniques, and outcomes of arthroplasties, comparison of preoperative characteristics of separate registries’ cohorts, and problems of the interpretation of information from other national arthroplasty registers when setting up a new registry.

Articles on studies with possible record linkage across registries: 2
Of these: potential studies on patient safety: 0
Of these: potential studies linking drug use & health status: 0

Collaboration/linkage between countries/registries (based on what is clear from abstracts):

- **European Arthroplasty Register (EAR)**
- **Multinational Global Orthopaedic Registry (GLORY)**
- **International Consortium of Orthopaedic Registries (ICOR)**
- **The International Spine Registry (SPINE TANGO)**
- **Nordic Arthroplasty Registry Association (NARA)**
- **USA**
- **Norway**
**Topic “Medical devices & Technologies”**

9 articles; 1988 - 2011. This topic is a special case since it includes articles which could also be grouped under other domains by the diseases/symptoms they concern. Grouping under this topic is decided by what seems to be the main focus of the articles.

Grouping based on article purpose/point:
Study (4), Registry (3), Study on registries (1), Unclassified (1)

Subtopics’ count where feasible: Medical devices & interventional procedures incl. implantable insulin delivery devices, drug eluting stents (3), Prostheses incl. breast implants, intraocular lenses & non-optical implants (2), Cardiovascular incl. coronary angiography, aneurysm repair; stent-graft techniques (2), Internal Medicine incl. renal failure treatment by conventional thrice-weekly hemodialysis (1), Fertility/Sterility incl. assisted reproduction technologies (1).

Study purposes where feasible:
There were three international registries found in the articles. The International Breast Implant Registry IBIR aims to integrate and replace the already existing national breast implant registries. The International Intraocular Lens and Implant Registry is a catalogue of intraocular lenses and non-optical implants from 33 manufacturers available to surgeons in 2003. The International Quotidian Hemodialysis Registry seeks to become the most important source of information required by governments, providers, and the nephrological community in assessing the utility of such therapies. The International Multicenter Registry of CT angiography CONFIRM investigates guidelines for the management of patients with suspected coronary artery disease. One article was about a study on the future of international registries for assisted reproductive technologies. Other studies were about implantable insulin delivery devices and a health technology assessment case study on drug eluting stents. The collaborators on advanced stent-graft techniques for aneurysm repair (GLOBALSTAR) project focused on aneurysm repair by stent-graft techniques. One unnamed international collaboration study discussed the collection and collation of data on new medical devices and interventional procedures.

| Articles on studies with possible record linkage across registries: | 0 |
| Of these: potential studies on patient safety: | 0 |
| Of these: potential studies linking drug use & health status: | 0 |

Collaboration/linkage between countries/registries (based on what is clear from abstracts):
| Articles on studies with possible record linkage across registries: | 0 |
| Of these: potential studies on patient safety: | 0 |
| Of these: potential studies linking drug use & health status: | 0 |

Collaboration/linkage between countries/registries (based on what is clear from abstracts):

- International Breast Implant Registry
- International Intraocular Lens and Implant Registry
- International Quotidian Hemodialysis Registry
- International Multicenter Registry of CT angiography CONFIRM
**Topic “Rare Diseases”**

4 articles, all focused on registries, published between 2005 – 2011.

International registry for primary hyperoxaluria, International registry on factor XIII deficiency, International Morquio A Registry, Global Rare Disease registry. Cystic fibrosis (2 references) could potentially be included in this group, but it is not really considered a rare disease in the European context.

**Topic “Renal Conditions”**

UK Renal Registry/USRDS (national registry, international comparisons) International Pediatric Peritonitis Registry, MOST (cyclosporine in renal graft survival).

**Conclusions from the literature review**

On the basis of the first stage of analysis of the included references’ abstracts, the following points are worth noting:

- The work of at least some APG representatives is clearly distinguishable amongst our references (eg. EUBIROD, EAR)
- Stem cell and bone marrow donor databanks/registries, as well as genetics registries are areas were significant international collaborative work is ongoing.
- We identified the model of ‘clinical studies’ registries. These studies are distinct from clinical trials (which, in principle were excluded from PARENT work). Clinical studies appear to be an alternative model to traditional registries. Hence when building the PARENT RoR, specific efforts should be made to engage them.
- Variability in the type of cross-border registry activity within each country, as well as variable formats of collaboration.

Reflecting back to the questions we have set to answer through reviewing the literature, it is apparent that at present we have obtained only partial answers. For some of the questions, additional information may arise during full text review of included publications or through complimentary desktop research. We do expect, however, that on certain topics academic publications may not provide the information we need. Particularly for topics such as those that constitute the focus of forthcoming work in WP6 – finance, governance and business models, as well as means and extend of achieving interoperability – other methods (e.g. interviews and surveys) may be more appropriate and fruitful.
# List of International Registries identified through WP6 Literature Review

<table>
<thead>
<tr>
<th>Registry Name</th>
<th>Clinical Domain</th>
<th>Registry Type</th>
<th>Year of establishment</th>
<th>Active/Stopped</th>
<th># of participating countries</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 International Association of Cancer Registries</td>
<td>Cancer</td>
<td>Registry Network</td>
<td>1966</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>2 International Registry of Tumor Immunotherapy</td>
<td>Cancer</td>
<td>Registry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Yogyakarta Pediatric Cancer Registry and Saskatchewan Cancer Registry</td>
<td>Cancer</td>
<td>Registry</td>
<td>2001</td>
<td></td>
<td>2: Indonesia, Canada</td>
</tr>
<tr>
<td>4 Breast Cancer Family Registry</td>
<td>Cancer</td>
<td>Registry</td>
<td>1995-2003</td>
<td></td>
<td>3: USA, Canada, Australia</td>
</tr>
<tr>
<td>5 Ireland-Northern Ireland-National Cancer Institute Cancer Consortium</td>
<td>Cancer</td>
<td>Programme</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7 Korean Hereditary Tumor Registry</td>
<td>Cancer</td>
<td>Registry</td>
<td></td>
<td></td>
<td>Korea</td>
</tr>
<tr>
<td>8 CT angiography; international Multicenter Registry CONFIRM</td>
<td>Cardiovascular Conditions</td>
<td>Clinical trials registry</td>
<td>2003</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>9 International Register of Potentially Toxic Chemicals IRPTC</td>
<td>Health threats</td>
<td>Registry</td>
<td>1973</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>Registry Name</td>
<td>Domain &amp; Subdomain</td>
<td>Year</td>
<td>Aged</td>
<td></td>
</tr>
<tr>
<td>-----</td>
<td>-------------------------------------------------------------------------------</td>
<td>--------------------------------------</td>
<td>--------</td>
<td>-----------</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>International Registry of Antiepileptic Drugs and Pregnancy EURAP</td>
<td>Health threats</td>
<td></td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>International Quotidian Hemodialysis Registry</td>
<td>Internal Medicine Registry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>International Breast Implant Registry IBIR</td>
<td>Medical Devices &amp; Technologies Registry</td>
<td>2002</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>International intraocular lens and implant registry</td>
<td>Medical Devices &amp; Technologies Registry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>5 cerebral palsy registers in UK</td>
<td>Neurology Registry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>International Online Registry for Organ Donation and Transplantation IRODaT</td>
<td>Organ Donation &amp; Transplantation Registry</td>
<td>1998</td>
<td>over 80</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Intestinal Transplant Registry</td>
<td>Organ Donation &amp; Transplantation Registry</td>
<td>1985</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>ISHLT Mechanical Assisted Circulatory Support Registry IMACS</td>
<td>Organ Donation &amp; Transplantation Registry</td>
<td>2013</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td>Registry of the International Society for Heart and Lung Transplantation</td>
<td>Organ Donation &amp; Transplantation Registry</td>
<td>1981</td>
<td>over 45</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>United Network for Organ Sharing UNOS, International Pancreas Transplant Registry IPTR</td>
<td>Organ Donation &amp; Transplantation Registry</td>
<td>Data from 1966</td>
<td>over 200 institutions</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Name</td>
<td>Type</td>
<td>Description</td>
<td></td>
<td></td>
</tr>
<tr>
<td>---</td>
<td>----------------------------------------------------------------------</td>
<td>------------------------------------</td>
<td>-----------------------------------------------------------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>20</td>
<td>US National Transplant Waiting List</td>
<td>Organ Donation &amp; Transplantation</td>
<td>Registry/Database</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21</td>
<td>European Arthroplasty Register EAR</td>
<td>Orthopaedics / Arthroplasty</td>
<td>Registry</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>22</td>
<td>Multinational Global Orthopaedic Registry GLORY</td>
<td>Orthopaedics / Arthroplasty</td>
<td>Registry</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>23</td>
<td>Nordic Arthroplasty Register Association NARA</td>
<td>Orthopaedics / Arthroplasty</td>
<td>Registry Network, 2007</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>24</td>
<td>Norwegian National Knee Ligament Registry NKLR, Kaiser Permanente</td>
<td>Orthopaedics / Arthroplasty</td>
<td>Registry, 2005-2011</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>25</td>
<td>Norwegian knee arthroplasty register, United States</td>
<td>Orthopaedics / Arthroplasty</td>
<td>Registry, (7-year follow-up)</td>
<td>2</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>International Consortium of Orthopaedic Registries ICOR</td>
<td>Orthopaedics / Arthroplasty</td>
<td>Registry Network</td>
<td></td>
<td></td>
</tr>
<tr>
<td>27</td>
<td>The international spine registry SPINE TANGO</td>
<td>Orthopaedics / Arthroplasty</td>
<td>Registry</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td>28</td>
<td>The International Clearinghouse for Birth Defects Surveillance and</td>
<td>Pregnancies / Congenital Anomalies</td>
<td>Registry Network, 1974</td>
<td>A</td>
<td></td>
</tr>
</tbody>
</table>

Foreign transplants received in 35 countries: Over 100 hospitals in 12 countries.
<table>
<thead>
<tr>
<th>No.</th>
<th>Description</th>
<th>Type</th>
<th>Date</th>
<th>Status</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>29</td>
<td>European Network of Congenital Anomaly Registers EUROCAT</td>
<td>Registry Network</td>
<td>1979</td>
<td>A</td>
<td>43 registries in 23 countries</td>
</tr>
<tr>
<td>30</td>
<td>The International Lamotrigine pregnancy registry</td>
<td>Registry</td>
<td>1992-2009</td>
<td>S</td>
<td>43</td>
</tr>
<tr>
<td>31</td>
<td>Bone Marrow Donors Worldwide BMDW</td>
<td>Registry Network</td>
<td>1988</td>
<td>A</td>
<td>67 stem cell donor registries from 49 countries, 47 cord blood banks from 31 countries</td>
</tr>
<tr>
<td>32</td>
<td>European Human Embryonic Stem Cell Registry</td>
<td>Registry</td>
<td>2007</td>
<td></td>
<td>Project ended, database accessible online</td>
</tr>
<tr>
<td>33</td>
<td>Registry of hES Cell Line Provenance</td>
<td>Registry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>34</td>
<td>International Stem Cell Registry of hES</td>
<td>Registry</td>
<td>2007</td>
<td></td>
<td></td>
</tr>
<tr>
<td>35</td>
<td>Bone Marrow Donors Worldwide BMDW: European Marrow Donor Information System Cord Blood Registry</td>
<td>Registry Network</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td>International Bone Marrow Transplant Registry</td>
<td>Registry</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
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<td>---</td>
<td></td>
</tr>
<tr>
<td><strong>37</strong></td>
<td>World Marrow Donor Association WMDA</td>
<td><strong>Stem Cell Donation &amp; Transplantation</strong></td>
<td>Registry Network</td>
<td>A</td>
<td></td>
</tr>
<tr>
<td><strong>38</strong></td>
<td>(Cord Blood Banks worldwide)</td>
<td><strong>Stem Cell Donation &amp; Transplantation</strong></td>
<td>Registry / Sample Bank Network</td>
<td>100 Cord Blood Banks worldwide</td>
<td></td>
</tr>
<tr>
<td><strong>39</strong></td>
<td>Japan Marrow Donor Program JMDP</td>
<td><strong>Stem Cell Donation &amp; Transplantation</strong></td>
<td>Registry (and network)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>40</strong></td>
<td>(European Bone Marrow Registries)</td>
<td><strong>Stem Cell Donation &amp; Transplantation</strong></td>
<td>Registry Network</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Information in blue font retrieved through direct online searches
Annex 4: Patient registries use cases in Directive 2011/24/EU: Rationale and stakeholders’ roles

Table 1. Article 12 - European Reference Networks

<table>
<thead>
<tr>
<th>Article #</th>
<th>Rationale</th>
<th>Stakeholders (Directive)</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.2 ERN objectives (at least 3 out of 8 to be fulfilled)</td>
<td>(a) highly specialised healthcare for patients and for healthcare systems by exploiting innovations in medical science and health technologies define the focus areas; (b) Pooling methodology/knowledge generation - presupposes some method of data collection and documentation - registries could be a tool; (c) registries could be the sources used to define what is “high-quality, accessible and cost-effective healthcare” (d) registries as a tool to follow up and study the cost effective use of resources; (e) Most explicit and in fact only direct reference to registries in the Directive - Context: epidemiologic surveillance; (g) Use of registry data for quality and safety benchmarking purposes – requirements have to be defined.</td>
<td>Healthcare providers and centers of expertise participating to the ERNs</td>
</tr>
<tr>
<td>12.4. List of specific criteria and conditions for ERNs and healthcare providers wishing to join. These criteria and conditions are given by means of delegated acts of the Commission. They shall ensure, for example, that ERNs (i) have knowledge and expertise to diagnose, follow-up and manage patients with evidence of good outcomes, as far as applicable; (ii) offer a high level of expertise and have the capacity to produce good practice guidelines and to implement outcome measures and quality control.</td>
<td>The sources of information for gaining evidence of good outcomes and for implementing outcome measures and quality control could be registries</td>
<td>European Commission: Adopts the specific criteria and conditions (in the form of delegated acts, as indicated in Art. 4.5)</td>
</tr>
</tbody>
</table>
Healthcare providers and centers: Must fulfil the expected conditions and criteria.

Registry holders: managing the sources of data
Patients: Improved outcomes and quality of care are to their benefit.
Insurers: Interest in cost-effective care

<table>
<thead>
<tr>
<th>Stakeholders (PARENT Interpretation)</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>In addition to the above:</td>
<td>National Healthcare authorities: epidemiologic surveillance, cost-effective use of resources</td>
<td>Registry holders: managing the sources of data</td>
</tr>
<tr>
<td>National Healthcare authorities: epidemiologic surveillance, cost-effective use of resources</td>
<td>Insurers: cost-effectiveness of care</td>
<td>Patients: Improved outcomes and quality of care are to their benefit.</td>
</tr>
<tr>
<td>Insurers: cost-effectiveness of care</td>
<td>Researchers/Research Community: b), d), e), g)</td>
<td>Insurers: Interest in cost-effective care</td>
</tr>
<tr>
<td>Professionals: involvement in all objectives as actors in services provision, also as researchers</td>
<td>Patients: recipients of high quality care [a), b), c)] – need to have own views reflected in monitoring methods (PROMs)</td>
<td></td>
</tr>
<tr>
<td>Patients: recipients of high quality care [a), b), c)] – need to have own views reflected in monitoring methods (PROMs)</td>
<td>Health technology industry: innovators, developing the respective technologies referred to in a)</td>
<td></td>
</tr>
</tbody>
</table>

NOTE: Recital 54 – ERNs to be focal points for medical training and research, information dissemination and evaluation, especially for rare diseases.
### Table 2. Article 15 - HTA: better evidence base for optimal use of new technologies

<table>
<thead>
<tr>
<th>Article #</th>
<th>15.1 Voluntary network of national authorities or bodies responsible for HTA ... shall be based on the principle of <strong>good governance</strong> including transparency, objectivity, independence of expertise, fairness of procedure and appropriate stakeholder consultations.</th>
<th>15.2 (b) Objectives of the HTA network shall be inter alia to support Member States in the provision of objective, reliable, timely, transparent, comparable and transferable information on the relative efficacy as well as on the short- and long-term effectiveness, when applicable, of health technologies</th>
<th>15.3 (b) In order to fulfil the objectives set out in paragraph 2, the network on health technology assessment may receive <strong>Union aid</strong>. Aid may be granted in order to inter alia support collaboration between Member States in <strong>developing and sharing methodologies for health technology assessment including relative effectiveness assessment</strong>.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rationale</strong></td>
<td>Principles of good governance - relevant as reference model for the development of sustainable business solutions for PARENT.</td>
<td>Registries as the source of real-world data to be used in studying the effectiveness of health technologies.</td>
<td>Possibly relevant for the sustainability and business planning of PARENT solutions - assuming registries are acknowledged as part of the methodologies for relative effectiveness assessment.</td>
</tr>
<tr>
<td><strong>Stakeholders (PARENT interpretation)</strong></td>
<td>PARENT JA and constituents of PARENT proposed solution after end of the JA: adopt and promote good governance standards</td>
<td>In addition to above: Researchers: As the performers of HTA research, producers of HTA information and potential users of registries. Registry holders: Registries as a</td>
<td>PARENT constituents and registry holders as providers of essential methodological component (registries) for relative effectiveness assessment</td>
</tr>
</tbody>
</table>

**Rationale**

- **Principles of good governance** - relevant as reference model for the development of sustainable business solutions for PARENT.
- **Registries as the source of real-world data** to be used in studying the effectiveness of health technologies.
- Possibly relevant for the sustainability and business planning of PARENT solutions - assuming registries are acknowledged as part of the methodologies for relative effectiveness assessment.

**Stakeholders (Directive)**

- **MS**: Appointment of national representatives
- **National HTA authorities or bodies**: Participating in the European health technology assessment network.
- **European Commission**: Supporting and facilitating cooperation among Member States.
- **HTA Network**: Supporting Member States, National Healthcare authorities and HTA Bodies
- **National Healthcare authorities**: Members and beneficiaries of the network
- **National HTA bodies**: Members and beneficiaries of the network
- **European Commission**: As the funder of the Network
- **National Healthcare Authorities**: Members and beneficiaries of the network
- **National HTA Bodies**: Members and beneficiaries of the network

**Stakeholders (PARENT interpretation)**

- **PARENT JA and constituents of PARENT proposed solution after end of the JA**: adopt and promote good governance standards
- In addition to above:
  - **Researchers**: As the performers of HTA research, producers of HTA information and potential users of registries.
  - **Registry holders**: Registries as a
potential source of real-world data to be used in studying the effectiveness of health technologies. Health technology industry: use of registries in assessment of technologies
Health Care Providers: As the potential performers of services and beneficiaries of the assessments. Insurers: reimbursement of effective technologies
Patients: As the potential beneficiaries of the assessments; also contribution to definition of assessment criteria and content.
### Table 3. Supporting patient's informed choice – Essential information on cross-border healthcare

<table>
<thead>
<tr>
<th>Article #</th>
<th>Rationale</th>
<th>Stakeholders (Directive)</th>
<th>Stakeholders (PARENT interpretation)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4.2b - Supporting patients' informed choice</td>
<td>Information of availability, quality and safety of healthcare (services) provided – potential link to indicator work. Will the source of information be registries or healthcare providers own databases? Potentially other authorities' databases responsible for monitoring? Either way, there will be a need for harmonization and coordination of data and information content (interoperability aspects).</td>
<td>Health care providers: producers and providers of information Patients: recipients of information and decision makers (selection of place of treatment)</td>
<td>Registries: potential source of information for aforementioned areas (of indicators) Healthcare professionals: documentation of pertinent data,</td>
</tr>
<tr>
<td>4.4. Non-discrimination in fees for care</td>
<td>MS are to ensure that same scale fees are applied to all patients, which implies ability to monitor and compare charges. Registries (in the sense of hospital/healthcare provider databases, other?) can be the source of pertinent information. Part of the main reasons and reasoning behind the HonCab project</td>
<td>MS: ensuring proper assignment of fees Healthcare providers: in the role of registry holders.</td>
<td>Registries: potential source of information for aforementioned areas (of indicators) Healthcare professionals: documentation of pertinent data, potentially also targets of assessment</td>
</tr>
<tr>
<td>6.3 Information to be provided through NCPs (National Contact Points)</td>
<td>In the PWC report, this article is used as reference for the mandatory nature of information provision on: Information regarding patients’ rights in [Member State], an overview of patients’ rights in [Member State] including patients’ right to choose his /her physician, receive information on treatment and quality and safety of healthcare in [Member State] (mortality, etc.), refuse treatment, privacy, access to (electronic) medical record, consent and sharing information, complaint procedures (in case of harm or reimbursement issues) etc. In such an interpretation, the same analysis holds as for Article 42.b.</td>
<td>Health care providers: producers and providers of information Patients: recipients of information and decision makers (selection of place of treatment)</td>
<td>Patients: beneficiaries of fair fee system Reimbursement bodies: control of expenditure, fair play.</td>
</tr>
</tbody>
</table>

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<table>
<thead>
<tr>
<th>Recital #</th>
<th>20</th>
<th>48 &amp; 49 (further details)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rationale</strong></td>
<td>Depending on what are the aspects of healthcare services that patients should be provided information on, there may be a role for registries as sources of information on eg. Patient safety, quality, waiting times.</td>
<td>Here the mechanism/organisational structure through which information will be made available to patients is defined (in the form of the National Contact Points) - Recital 49 provides additional 'instructions' on the profile of the NCPs.</td>
</tr>
<tr>
<td><strong>Stakeholders</strong></td>
<td>HC providers, patients, professionals, authorities, policy makers, NCPs</td>
<td>HC service providers, professionals, patients, health technology industry, policy makers, authorities</td>
</tr>
</tbody>
</table>
Annex 5: Items in Directive 2011/24/EU of relevance for PARENT Joint Action work

Table 1: Interoperability aspects – overview of pertinent Articles

<table>
<thead>
<tr>
<th>Article</th>
<th>Rationale</th>
<th>Stakeholders</th>
</tr>
</thead>
<tbody>
<tr>
<td>11 Mutual recognition of prescriptions (and medical devices)</td>
<td>Interoperability and standardization (incl. respective infrastructure) being developed/used in the context of mutual recognition of prescriptions will be of relevance for registries, too particularly with regard to data sets, medicines and medical device monitoring – e.g. (c) measures to facilitate the correct identification of medicinal products or medical devices prescribed in one Member State and dispensed in another, including measures to address patient safety.</td>
<td>MS: legal framework, role</td>
</tr>
<tr>
<td>4.2.e right to privacy with respect to the processing of personal data</td>
<td>One of the key requirements for any data sharing, including registry data</td>
<td>MS of</td>
</tr>
<tr>
<td>4.2f and 5d copy of medical record of treatment / copy of medical records to ensure continuity of care</td>
<td>Content of medical record will (eventually) be based on the minimum data set (recently endorsed by eHN), which should also form the basis for the PARENT minimum data set.</td>
<td>MS of treatment</td>
</tr>
<tr>
<td>14.2.a Objectives of eHealth Network – incl. sustainability &amp; interoperability of eHealth applications</td>
<td>sustainability (focus on economic and social), interoperability, support to the goals of safe and high quality healthcare. PARENT needs to provide a sustainable solution ensuring interoperability of patient registry data across EU Member States</td>
<td>MS Policy makers</td>
</tr>
<tr>
<td>14.2.bi Minimum data set, patient safety in the cross-border setting</td>
<td>PARENT should build its recommendations to MS registries around the use and utilization of the minimum data set</td>
<td>MS Policy makers</td>
</tr>
<tr>
<td>14.2.c Common identification and authentication measures</td>
<td>Relevant in so far as it enables identification of individuals (when necessary) in registry data, potentially also in solutions for remote access to data</td>
<td></td>
</tr>
</tbody>
</table>
both as a state of treatment and affiliation
EC: adoption of INN and dosage of medicinal products

<p>| Stakeholders (PARENT interpretation) | Industry: pharmaceuticals, devices | Registry holders: means for unique identification of medicinal products and devices | Patients: stand to benefit from a smoothly operating system | Healthcare providers: necessary provisions for protection of sensitive data Registry holders authorities, Researchers: users of data Patients: Data subjects |
|-------------------------------------|-----------------------------------|---------------------------------------------------------------------------------|-------------------------------------------------|-------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------|
| Treatment                          | (42f) MS of affiliation (5)       | appointed to the eHealth Network                                                | appointed to the eHealth Network                | Healthcare providers: Ensure acquisitions of suitable documentation systems, establish necessary processes Health care professionals: users of IT-systems, direct contact with patient and provision of record IT-companies: incorporate minimum data set in eHealth applications, Authorities: NCP management, MoH, national/regional eHealth/IT-coordinating centers (various roles) Patients: recipients of records Registry holders: utilization of minimum data set industry, hc provider organisations, patients, hc professionals, industry (health- IT and other technologies). |</p>
<table>
<thead>
<tr>
<th>Topic</th>
<th>Article references</th>
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<tr>
<td>organization, delivery and financing of care</td>
<td>1.1, 1.4, 12.6</td>
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<tr>
<td>Legislation, standards and guidelines on quality and safety of Member</td>
<td>4.1.</td>
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<td>state of treatment</td>
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<td>Extend of information provided to patients</td>
<td>4.2b</td>
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<td>Privacy and data protection laws</td>
<td>4.2.e, 4.2.f, 5, 14.2</td>
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<td>Complaint procedures and mechanisms for seeking remedies</td>
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<tr>
<td>Participation of members to ERNs/HTA network</td>
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