HOW TO ENHANCE RARE DISEASE (RD) RESEARCH (IN NORDIC COUNTRIES)?

SHARING A FINNISH VISION

Mikko Seppänen M.D., Ph.D., Docent in Internal Medicine

Specialist in Internal Medicine and Infectious Diseases, FCIS (USA)

Chief Physician, Rare Diseases Center

Head Physician, Pediatric Research

Children and Adolescents, HUS Helsinki University Hospital

- No financial liabilities

- Conflicted towards RD and genetic diseases...
  - HUS Rare Diseases Center, Chief Physician/Director, with 25+ years of clinical RD experience ("Clinical Immunologist")
  - Member, Working Group for the Finnish RD Coordinating Center
  - Inborn Errors of Immunity (IEI) Group PI (=RDs)
- Chair
  - Doctoral Committee, Faculty of Medicine, University of Helsinki
  - European Society for Immunodeficiencies (ESID) Registry (until Oct 2022)
- Member
  - ESID Board (until Oct 2022)
  - Clinical Immunology Society (CIS, US)
  - International Union of Immunological Societies (IUIS) IEI Expert Committee
  - ClinGen (US) IEI Clinical Domain Working Group Executive Committee
  - International Association of Primary Immunodeficiency Societies (IAPIDS) Board

WHAT CAN WE LEARN FROM EACH OTHER – POTENTIAL ADVANTAGES IN NORDIC COLLABORATION

JOINT NORDIC POPULATION is only approximately 27,3 M

- equals 3x Greater London area, less than 50% of UK / French populations)

Beneficial collaboration of Nordic countries should accomplish something we cannot readily get from European Reference Network collaboration alone

What will the European Reference Networks provide?

ON AIMS OF ERNs

AIMS WORTHWHILE

Collaboration

- Guidelines
- Training
- Facilitation of large clinical studies
  - new drugs, new medical devices
  - new care models, eHealth solutions and tools

Sharing of knowledge and data

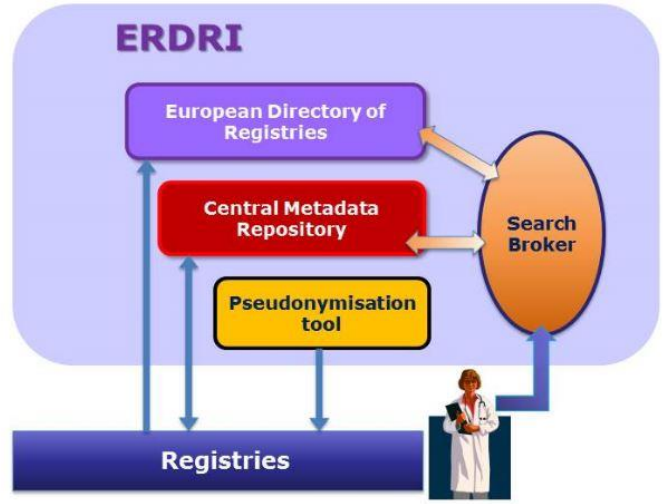
- Clinical consultations
- Quality registry data with follow up (European Health Data Space)

"the wider the better"

TOOLS AND LIMITATIONS

Clinical Patient Management System (CPMS)*

- compatibility with EEA data protection legislation?
- complex and laborious to use



ERN Registries*

- compatibility of "mother registries" with GDPR?
  - duration of data storage, data minimisation, specified purpose vs.repurposing vs. local interpretations
  - EDPB in general against "broad consent" (= lax interpretation of specificity of purpose) and indefinite/ long-term storage
- patient consent → important data left out, especially on treatment failures
- only 16 common data elements →?

ORPHAcodes

- still very scarcely implemented anywhere in EU, but partly built in into ICD-11

* Under Commission Data Protection Regulation 2017/46– NOT GDPR & based on patient consent.
For recent EDPB renditions, see EDPB document 2nd Febr 2021 on health research

MEANS STILL MEAGER

Financial issues still remain largely unsolved

- Allocation based on equal sums or time spent vs. local purchasing power?
- Who pays? Commission, state, healthcare provider, all?
- Collaboration with pharmaceutical companies?

How to legitimize the time and effort into ERNs for the Healthcare Provider?

European Health Data Space and interoperability

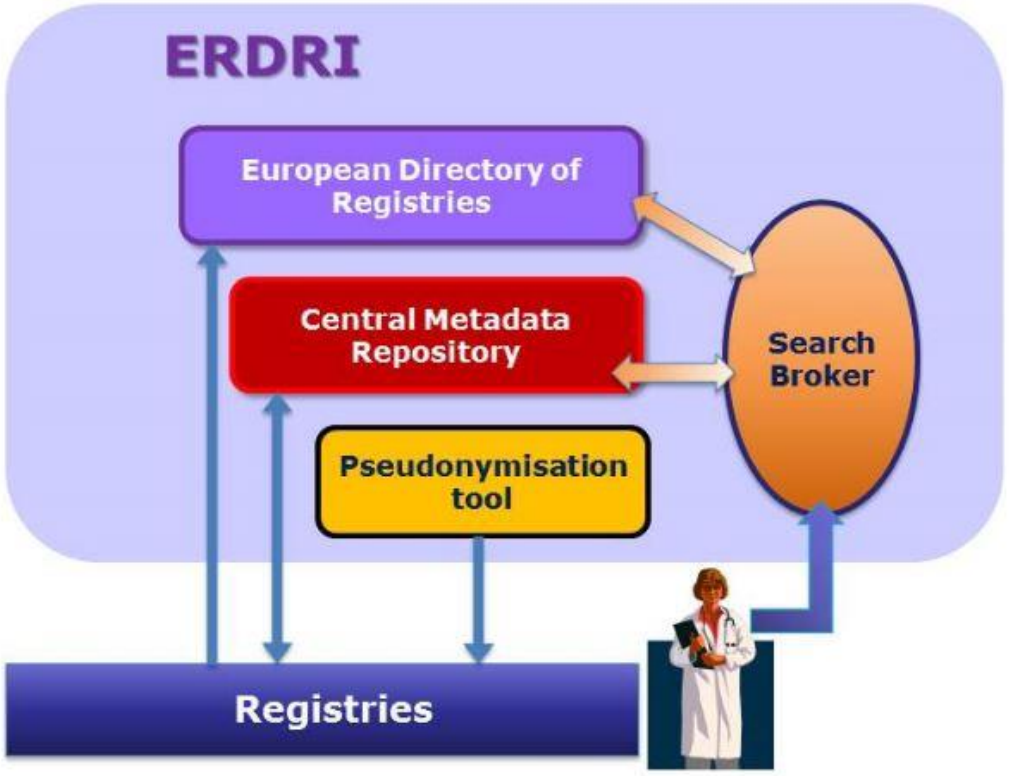
HUS

...have strengths and weaknesses

ERN REGISTRIES

EUROPEAN PLATFORM ON RARE DISEASE REGISTRATION (EU RD PLATFORM)

- Launched 2019
- European RD Registry Infrastructure (ERDRI) contains
  - tools that render the data of existing registries FAIR (Findable, accessible, interoperable, reusable)
  - the set of common data elements for Rare Diseases Registration
  - European Directory of Registries (ERDRI.dor)
  - Central Metadata Repository (ERDRI.mdr)
  - Search broker (ERDRI.sebro) allows “any user” to retrieve metadata of interest
  - pseudonymisation tool



PATIENT CONSENT FORM FOR DATA SHARING
in
EUROPEAN REFERENCE NETWORKS FOR RARE DISEASES
for
PATIENT CARE and CREATION OF RARE DISEASE REGISTRIES

WHAT ARE THE EUROPEAN REFERENCE NETWORKS AND HOW CAN THEY HELP ME?

- European Reference Networks (ERNs) are networks of healthcare professionals working in rare diseases across Europe. They are established by Directive 2011/24/EU on the application of patients' rights in cross-border healthcare.
- ERNs exist to allow healthcare professionals to work together to support patients with rare conditions or other conditions which need highly specialized therapeutic procedures.
- With your consent, and in accordance with national and European data protection laws, your case may be referred to the ERN(s) named overleaf, so that the healthcare professionals in the ERN may help your doctor develop your diagnosis and care plan.
- In order for the ERN to advise on your care, the data collected about you in this hospital needs to be shared with healthcare professionals in other hospitals, some of which may be in other European countries. Your doctor can tell you more about which countries are in the ERN(s) relevant to your condition.
- Your care will remain the responsibility of the healthcare professionals who usually look after you.
- Data about you will not be shared without your consent, and even if you choose not to give your consent your doctors will continue to take care of you to the best of their ability.

PATIENT DATA SHARED FOR CARE WILL BE DE-IDENTIFIED

- If you and your doctors agree that it would be good to ask for support from one or more ERNs, this consent form will allow this hospital to share any of the data stored in your health care record which would help the healthcare professional in the ERN(s) to discuss your care.
- Your name and address will not be included.
- Such data may include medical images, laboratory reports, as well as biological sample data. It may also include letters and reports from other doctors who have cared for you in the past.
- If ERN(s) are consulted for your care, your data will be shared through a secure electronic information system called the ERN Clinical Patient Management System.

WHAT ABOUT RARE DISEASE DATABASES /REGISTRIES?

- To improve future knowledge on rare diseases, ERNs are very dependent on databases of information for research and knowledge development.
- Databases, also known as registries, contain only de-identified information. Your name, full date of birth or address are NOT included, only information about your condition.
- To help build the databases, you may give your consent for your data to be added to such databases. If you choose not give your consent this will not affect your care.

WHAT ABOUT RARE DISEASES RESEARCH?

- You may also let us know if you would like to be contacted about research projects for which your data could be used.
- If you agree to share your data for research you will be contacted to provide consent for a specific research project.
- Your data will not be used for research without your specific consent for a named research project.

WHAT ARE MY RIGHTS?

- You have the right to give or withhold your consent to sharing data in the ERN(s).
- If you consent today you may withdraw your consent later. Your doctor will explain how data about you can be removed from records if you wish. It may not be possible to remove information that has been used to care for you.
- You are entitled to receive further information about the purposes for which your data will be processed and who will have access to it. Your doctor can tell who can help you if you would like more information.
- You have a right to see which data is stored about you and to have corrections made to any errors you find. You may also have the right to block or erase your data.
- The hospital where your data is collected is responsible for your data. It should address your requests concerning your data in 30 days.
- It has the duty to ensure your data is processed safely and to notify you if a breach of data security occurs.
- If you have any concerns about the way in which your data is processed you may contact your treating doctor or your relevant data protection authority
- The need for keeping your data in the ERNs will be reviewed by your hospital every 15 years.

THIS CONSENT FORM MAY BE USED FOR SHARING DATA WITH THE FOLLOWING ERN(S)

(To be completed by the health care professional signing below)

.....

.....

.....

PATIENT DETAILS

First Name: ..... **Surname:** .....

Date of Birth: ☐☐ ☐☐ ☐☐☐☐ (D D M M Y Y Y Y) **ID number:** ☐☐☐☐☐☐☐☐☐☐

Please tick the box that applies:

☐ **I am the patient** ☐ **I am the parent/guardian of the patient** ☐ **I have power of attorney**

☑ ***I CONSENT to my de-identified data being shared in ERN(s) for my CARE***
I understand that my data will be shared with healthcare professionals in the ERN (s) so that they may work together to support my care.
Signature **Date**
....

☒ ***I DO NOT CONSENT to my data being shared in ERN(s) for my CARE***
I understand that this means the ERN(s) cannot be consulted to support my care.
Signature **Date**
....

☑ ***I CONSENT*** *to my de-identified data being included in one or more ERN database or registry.*
Signature **Date**
....

☒ ***I DO NOT CONSENT*** *to my data being included in an ERN database or registry.*
Signature **Date**
....

☑ ***I WOULD LIKE TO BE CONTACTED*** *about research. I will decide if I consent to my data being used for a specific project if I am contacted.*
Signature **Date**
....

☒ ***I DO NOT WANT TO BE CONTACTED*** *about my data being used in research.*
Signature **Date**
....

TREATING PHYSICIAN or PERSON AUTHORISED TO WITNESS CONSENT

Name ..... **Position** ..... **Date** .....

EUROPEAN PLATFORM ON RARE DISEASE REGISTRATION (EU RD Platform)

SET OF COMMON DATA ELEMENTS FOR RARE DISEASES REGISTRATION

GROUP	ELEMENT N°	ELEMENT NAME	ELEMENT DESCRIPTION	CODING	COMMENT
1. Pseudonym	1.1.	Pseudonym	Patient's pseudonym	• String	https://eu-rd-platform.jrc.ec.europa.eu/erdri/eupid-intro
2. Personal information	2.1.	Date of birth	Patient's date of birth	• Date (dd/mm/yyyy)	
	2.2.	Sex	Patient's sex at birth	• Female • Male • Undetermined • Foetus (Unknown)	
3. Patient Status	3.1.	Patient's status	Patient alive or dead	• Alive • Dead • Lost in follow-up • Opted-out	If dead then answer question 3.2
	3.2.	Date of death	Patient's date of death	• Date (dd/mm/yyyy)	
4. Care pathway	4.1.	First contact with specialised centre	Date of first contact with specialised centre	• Date (dd/mm/yyyy)	

5. Disease history	5.1.	Age at onset	Age at which symptoms/signs first appeared	• Antenatal • At birth • Date (dd/mm/yyyy) • Undetermined		retrospective data
	5.2.	Age at diagnosis	Age at which diagnosis was made	• Antenatal • At birth • Date (dd/mm/yyyy) • Undetermined		
6 Diagnosis	6.1.	Diagnosis of the rare disease	Diagnosis retained by the specialised centre	Orpha code (strongly recommended – see link) / Alpha code/ ICD-9 code/ ICD-9-CM code / ICD-10 code	http://www.orphadata.org/cgi-bin/inc/product1.inc.php	
	6.2.	Genetic diagnosis	Genetic diagnosis retained by the specialised centre	International classification of mutations (HGVS) (strongly recommended – see link) / HGNC / OMIM code	http://www.hgvs.org	deletions, chromosomal defects, other complex genetic diseases?
	6.3	Undiagnosed case	How the undiagnosed case is defined	• Phenotype (HPO) • Genotype (HGVS)		HPO still work in progress
7. Research	7.1.	Agreement to be contacted for research purposes	Patient's permission exists for being contacted for research purposes	• YES • NO		legal status?
	7.2.	Consent to the reuse of data	Patient's consent exists for his/her data to be reused for other research purposes	• YES • NO		legal status?
	7.3.	Biological sample	Patient's biological sample available for research	• YES • NO	If YES answer question 7.4	legal status?
	7.4.	Link to a biobank	Biological sample stored in a biobank	• YES (if appropriate use link) • NO	https://directory.bbmri-eric.eu	legal status?
8.Disability	8.1.	Classification of functioning/disability	Patient's disability profile according to International Classification of Functioning and Disability (ICF)	• Disability profile / Score	http://www.who.int/classifications/icf/whodasii/en/	complicated, arduous, depends on investigator- why not PROM(IS)?

ERN REGISTRIES WILL – FOR THE TIME BEING BE…

- purely epidemiologic registries
- laborious point of entries into studies with separate consents
- will face plenty of legal hurdles vs. Members States & European Data Protection Board (EDPB) before GDPR/EDPB-defined SPECIFIC PURPOSE, REPURPOSING, TIME-LIMITED STORAGE and SUBSERVIENT CONSENT are solved to evolve into EU-wide quality registries

- Scientific mother registries of metaregistries will
  - continue to face challenges vs. GDPR and EDPB
  - be capable of true quality registry work to an extent, but their data is imperfect, incomplete, insufficient, laborious and costly (manual data entry, compliance)

What's in the word, joint strengths?

"NORDIC"?

NORDIC COUNTRIES SHARE 1

Large geographic areas with geographic barriers to gene flow, sparse populations and founder effects

- Finnish Disease Heritage, Icelandic founder variants, Danish founder variants, Norwegian founder pockets, Swedish Dalarna county founder pocket

Rather similar genetic roots with variable admixture of shared influences by

- European (Western & Eastern) Hunter-Gatherers, early European Farmers, Jamna nomads
- Gene flow from Sami people
- Asian-Uralic consecutive gene flow events from Northern and Middle Eastern Asia (likely since 7000-8000 years ago bringing locals fair skin)

NORDIC COUNTRIES SHARE 2

Shared history resulting in rather similar governmental and legal frameworks

Universal healthcare, i.e. the ”Nordic welfare states”

Exceptionally educated populations

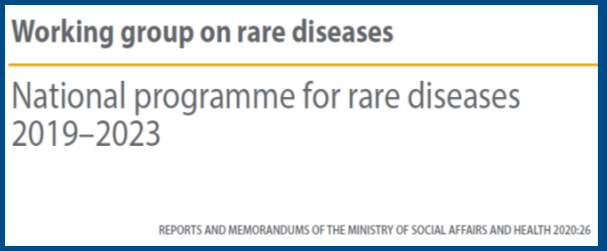
”Overlapping” languages

Exceptionally ”happy” populations = trust in officials, in science and in healthcare equity

Exceptionally comprehensive public and electronic healthcare records with somewhat reliable (ICD-10) data entry and handling

What do we need to facilitate RD trials?

UNIFORM PLANS ?



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DRUG DEVELOPMENT AND RDs

- Discovery
  - granularly chosen, uniform cohorts with sufficient N and sample availability
  - translational research to unravel biomedical etiopathogenesis, genes involved, "human knock outs" and their primary cells
- Development
  - translational laboratory and biobank discovery and cellular studies (cell models, primary cells)
- Preclinical Research
  - animal and *in vitro* a.o. primary cell-based studies for basic safety
- Clinical Research
  - comprehensive recruitment and surveillance, outcome measures
- EMA Review and Approval
- EMA Postmarketing Safety Surveillance Studies
  - comprehensive follow up, WITHOUT patient consent

Uniform & granular national RD coding (ORPHA, gene)

National RD registries (w/o patient consent)

Collaborating RD patient organizations

Collaborating biobanks & researchers (w patient consent)

Quality registries for a.o. postmarketing s. (w/o patient consent)

ORPHA CODES

CURRENT

- Finland: ORPHA coding used in regional RD Registries in 2 biggest hospitals

PLANNED

- National, obligatory ORPHAcoding in specialist care
- Short ORPHAcode versions available at the National Code Server
- Piloting will commence in HUS HUH 1st Q 2023
- National Institute of Health and Welfare (THL) maintains
  - national EPR qualifications in HC
  - HILMO = Care Register for Healthcare
    (Care Notification Data System)

REGISTRIES – THE TRADITIONAL STRENGTH OF NORDIC COUNTRIES

ERN registries will be epidemiological registries and points of entry

- since they mostly rely on ”mother registries”, the discrepancies between GDPR and Commission Data Protection Regulation will cause problems
- cannot soon grow into true quality registries

In Nordic countries, nationwide ORPHAcoding and EPRs → registries close to true quality registries

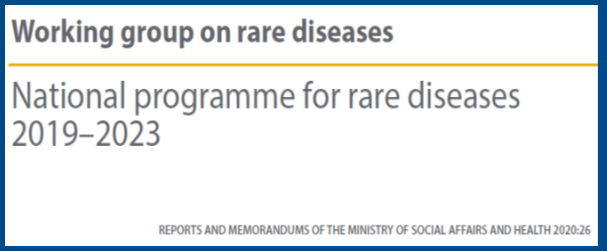
- official, legal
- collaboration for interoperability?

A national quality registry contains person-based details relating to a problem, the actions taken and the results within the health and care services.

A fully-developed quality registry enables follow-up of the health care of all patients in a given disease group

What do we need to facilitate RD trials?

PLANS IN FINLAND



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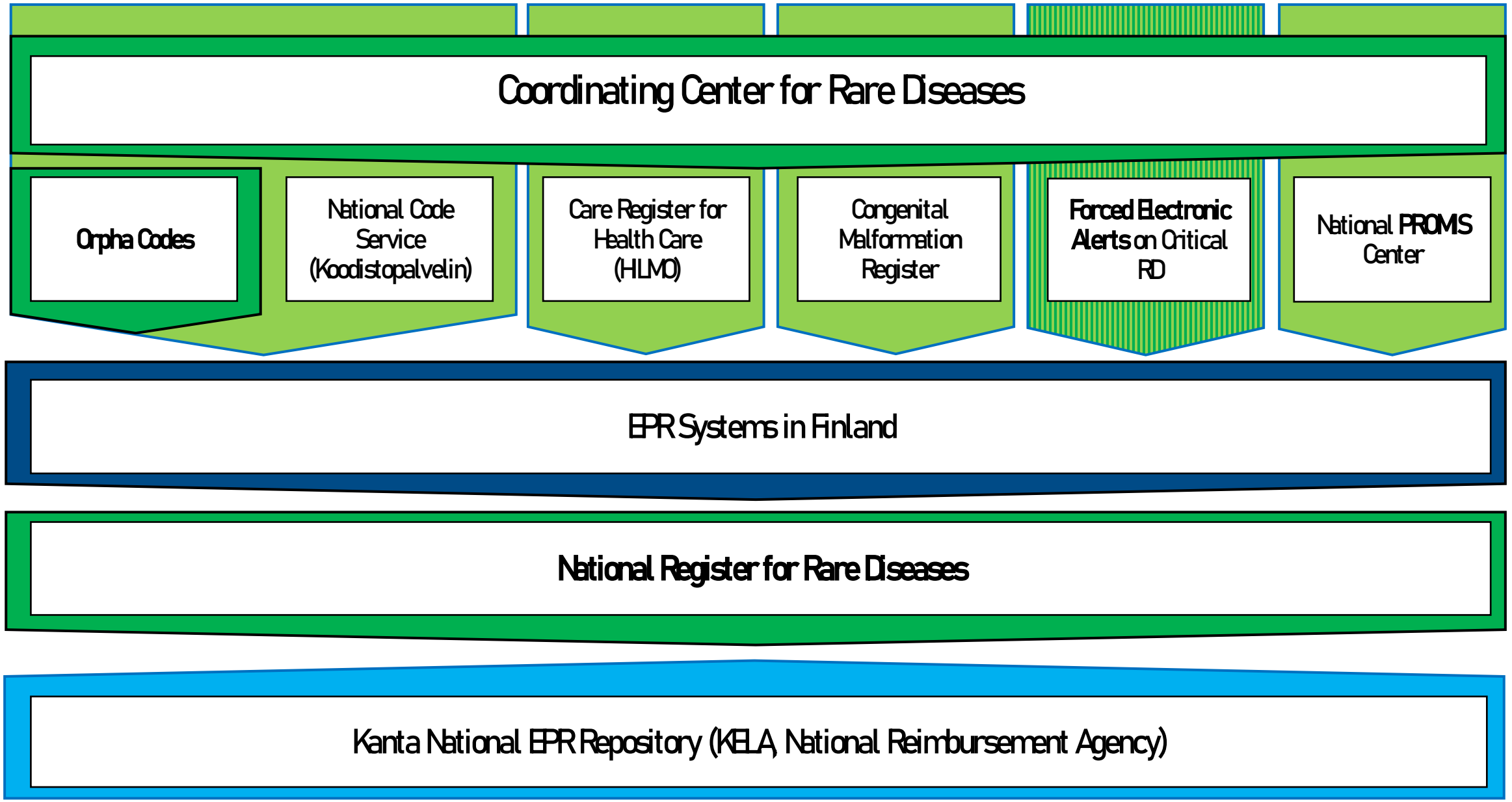

PROJECTED TIMELINE

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- We expect to...
  - start Orpha coding nationally by 2024-25
  - codes activated by Expert Physicians
- Plans...
  - RD Orpha Code once / patient
    - effective until otherwise assessed and amended by an expert physician in the field
  - Physicians will likely use
    - National Code Server within EPR
    - (& on demand Orphanet's Orpha Diseases Server in parallel for ultrarare diseases)

NATIONAL RD COORDINATING CENTER

Finnish institute for health and welfare

- Orpha Code will activate
  - inclusion into National RD Registry
  - → later also forced Electronic Alerts for chosen few
    - RD experts will need to format and regularly update National Emergency Treatment Guidelines
- Codes will be visible in all EPR systems and the National Hospital Discharge Registry
  - for all visits (!)
  - to the patient in EPR and Kanta Repository:
    - numeric code
      - ORPHA 2863
        Short stature-wormian bones-dextrocardia syndrome (aka Stratton-Parker syndrome)

"WHERE IS THE BEEF"

FOR NORDIC COLLABORATION BEYOND SHARING EXPERIENCES?

Only governmental, national RD registries w/o separate consents can tackle these challenges

- Only Nordic countries with national registries could potentially overcome these problems – as well as collaborate???
- Automated data entries, universal or wide coverage, EPRs, existing infrastructure, population attitudes favorable, maybe even same RD registry frames…??

JOINT NORDIC POPULATION is 27,3 M (3x Greater London area, less than 50% of UK or French populations)

OTHER WORTHWHILE WAYS TO COLLABORATE, OVERSEE AND FACILITATE ERN INTEGRATION?