RARE DISEASE REGISTRIES
AIMS, SUSTAINABILITY
and GOVERNANCE

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Outline

• Aims:
  – Disease or diseases? What type of registry would fit?

• Governance:
  – Networking people
  – Linking data from heterogeneous sources, favoring interoperability

• Sustainability:
Epidemiological studies

analytical

Controlled
- Randomized trials
- Non-randomized studies

Not controlled
- Phase I or phase II trials
- Cohort
- Registry
- Case-control
- Case reports
- Series of cases

observational

descriptive
A cohort study proceeds from exposure to outcome.

Investigators identify a group with an exposure of interest and another group(s) without the exposure.

The investigators follow forward in time the exposed and unexposed groups to determine outcomes.

If the exposed group develops a higher incidence of the outcome than the unexposed, then the exposure is associated with an increased risk of the outcome.

A cohort study enables calculation of incidence rates, relative risks, and attributable risks (whether causality is demonstrated).

However, for the study of rare events, this type of research design can be slow to yield results and in some cases be prohibitively expensive.
RaDiCo commits at the heart of the European and international projects

Horizon 2020 and other international and European cooperation programs are the core of RaDiCo platform deployment strategy

Learn more

www.radico.fr
### 16 national and European cohorts

<table>
<thead>
<tr>
<th>Cohort Name</th>
<th>Description</th>
<th>Principal Investigators</th>
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<tr>
<td>RaDiCo-ACŒIL Cohort</td>
<td>National cohort on congenital defects of the eye: natural history, genetic determinisms and improved ocular and extra-ocular outcome prediction for better patient management</td>
<td>Patrick Calvas, Nicolas Chassaing</td>
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<tr>
<td>RaDiCo-ACOSTILL Cohort</td>
<td>National cohort on adult and childhood onset Still disease</td>
<td>Sophie Georgin-Lavialle</td>
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<td>RaDiCo-COBBALT Cohort</td>
<td>National cohort on Bardet-Biedl syndrome and Alström syndromes</td>
<td>Hélène Dollfus</td>
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<td>RaDiCo-COLPAC Cohort</td>
<td>National cohort on the epidemiology, clinical and genetic heterogeneity of Low Phospholipid-Associated Cholelithiasis (LPAC) syndrome</td>
<td>Christophe Corpechot</td>
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<tr>
<td>RaDiCo-ECYSCO Cohort</td>
<td>European cystinosis cohort</td>
<td>Aude Servais</td>
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<tr>
<td>RaDiCo-EURBIO- Alport Cohort</td>
<td>European cohort on Alport Syndrome: search of prognostic biomarkers</td>
<td>Laurence Heidet, Bertrand Knebelmann</td>
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<tr>
<td>RaDiCo-FARD Cohort</td>
<td>National cohort for the evaluation of individual burden in the course of rare skin diseases</td>
<td>Christine Bodemer</td>
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<td>RaDiCo-GenIDDA Cohort</td>
<td>International social network for data collection on the natural history of rare monogenic forms of intellectual disabilities</td>
<td>Jean-Louis Mandel</td>
</tr>
<tr>
<td>RaDiCo-IDMet Cohort</td>
<td>National and European cohort on Imprinting Disorders and their metabolic consequences</td>
<td>Agnès Linglart, Irène Netchine</td>
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<tr>
<td>RaDiCo-MARFAN Cohort</td>
<td>National cohort on Marfan syndrome and related diseases</td>
<td>Guillaume Jondeau</td>
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<tr>
<td>RaDiCo-MPS Cohort</td>
<td>National cohort on mucopolysaccharidosis in the era of specific therapeutics</td>
<td>Bénédicte Héron</td>
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<tr>
<td>RaDiCo-PCD Cohort</td>
<td>National cohort on Primary Ciliary Dyskinesia: Identification of specific severity criteria and phenotype-genotype correlation study</td>
<td>Estelle Escudier</td>
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<td>RaDiCo-PP Cohort</td>
<td>National cohort on periodic paralysis: clinical, genetic and medico-economic studies involving m-health monitoring tools</td>
<td>Savine Vicart</td>
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<tr>
<td>RaDiCo-PID Cohort</td>
<td>National cohort on Idiopathic Interstitial Pneumonia from infancy to elderly: genetic and environmental determinants</td>
<td>Annick Clement</td>
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<tr>
<td>RaDiCo-RETICO Cohort</td>
<td>National cohort on inherited retinal dystrophies</td>
<td>Hélène Dollfus</td>
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<tr>
<td>RaDiCo-SED-VASC Cohort</td>
<td>National cohort on vascular Ehlers-Danlos syndrome</td>
<td>Xavier Jeunemaître</td>
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Patient registry (1)

An organized program using *observational* study methods for the collection, storage, retrieval, and use of a clearly defined *set of data* on identifiable *individuals* or a *population* defined by a particular *disease*, condition, or exposure, to evaluate specified *outcomes* ...

Patient registry (2)

... for one or more predetermined scientific, clinical, or policy purpose(s) such as:
- public health surveillance,
- epidemiological and longitudinal research,
- patient education, research recruitment,
- or population safety monitoring for post-marketed drugs or devices.

A registry database is a file (or files) derived from the registry.
Population – based registry

“A continuous and comprehensive collection of personal data, concerning one or more health events, in a geographically defined population, for research and public health purposes, managed by a team with the appropriate skills.“

Source: French decree of November 6, 1995 relative the National Committee of Registries
Pop-based versus non pop-based registries

- Population-based registries, refer to a *geographically* defined population and aim to register *all* cases in that population,

- Non-population-based registries are based on selected bodies, clinical centers or other types of structures (members of a patient organization, participants registered via an ERN or other disease-specific registry, ..) where the population coverage may *not* be comprehensive.

- These two types of registries have different uses but both are useful, provided they serve identified targeted aims.

- Multiple RD registries (> 600) already exist in Europe.

(Source: Disease Registries in Europe, Orphanet Report Series, RD Collection, 2013)
Patient registry: general considerations

- Are not sufficient for population-based estimates of disease,
- Used to estimate the numbers of affected patients
- Importance to clearly define the registry objectives
- Together with realistic expectations
- and carefully consider models that are flexible and cost-effective
- Setting up a registry is expensive,
- requires long-term commitment for their development and sustainability.
- Multi-disciplinary knowledge, shared resources and infrastructure are to be privileged,
- Looking for providing benefit at reasonable costs.

Source: ibidem
Governance

• Network people
• Organize the network
  – patients and professionals
  – data
• Define the purposes
• Network the centers of reference/competence
Network people

• Identify key stakeholders and set up a Registry Advisory Committee
• Organize the registry platform
Set up a registry Advisory Committee

- Advisory Committee should include
- Disease experts
- Experts in registry design/analysis
- Epidemiologists
- Representatives of patients, patient advocacy group(s), disease foundations
- Representatives of pharmaceutic companies when appropriate
- Other stakeholders according to the specificity of the registry
Define the purposes of the registry

- *Observational* research in a *population*, describe natural history of a disease/condition
- Locates and lists patients/facilitates the networking
- Supports the generation of new hypotheses,
- Provides *preliminary data* for future clinical trials,
- Useful to estimate the number of available patients to *guide study planning*.
- Enables identifying patients *eligible* for clinical trials,
- Helps drug development
- Enables patients reporting outcomes,
- Improves clinical care and establish evidence-based medical practices
Foster patient participation, outreach activities and patient advocacy

- Establish *community trust*, and *ensure follow-up* over time
- Develop *inventory* of registries outlining their scope, any *existing* resources that might be shared and *quality assessment*
- Find ways to provide *incentives* to clinicians and *reduce costs* of data entries
- Establish a one-stop *listing of resources* and *best practices*
- Explore the *dissemination* of information and *guidance*
- Write a registry *manual* for « Dummies »

Network data

• Identify the patients via a Global Unique Identifier
• Define the target population and inclusion/ non-inclusion criteria
• Write the registry protocol, policies, case report forms, data monitoring and data management plan
• Design data collection tools
• Foster interoperability
A RD national identifier

- Generate a *unique* and *anonymous identifier* for RD, according to the regulations in force, given the specific restrictions defined by the CNIL (limited access to the NIR)
- Enable sharing *de-identified* data
- Reduce the number of duplicates (two IDs for a single patient) and potential collisions (same ID for two different patients)
- Enable following patients over time
- Such an approach has already been carried out by the Global RD patients Registry (GRDR) USA: the *Globally Unique Identifier* (GUID).
Clinical Research, Patient Care & Disease Management

• Proceed step by step to develop a coordinated registry
• Use existing applications
• Evaluate existing models
• Network the centers of reference/competence

Interoperability

- It is based on standards and/or controlled vocabularies that promotes communication with other information systems.

- For information technology or systems engineering services interoperability allows information exchange.

- Interoperability for data and systems is crucial for exchanging information.
An interoperability framework for RD
The French Hub for RDs

- Define the data set via a **consensus** among all healthcare RD professionals, and stakeholders for **all rare diseases**;
- Define a national **interoperability framework** compatible with EHRs;
- Register patients **at the heart of care** activities;
- **Propagate** the information to epidemiology and research databases;
- Use **information technology** tools and methods
- **Connect** the RDs centers;
- Set up the **French Information Hub for RDs**
The French RD Information Hub

**Objectives**

- **Public Health**
  - Epidemiology
- **Patients support of care**
- **Clinical trials Cohorts**

**Systems**

- BNDMR
- EHR
- MDS
- RaDiCo

**Domains**

- Public Health
- Care
- Research

**Infrastructures**

- BNDMR, PNMR2, DGOS, DGS
- Plan Hôpital Numérique, DGOS, DGS, ARS
- RaDiCo, investments for the future, INSERM, ANR

**Connectors**

- Interoperability framework
- Interoperability of systems and data

**Sources**

- Landais P, Choquet R, BaMaRa 2014

**Abbreviations**

- BNDMR: National Data Bank for Rare Diseases
- BaMaRa: Rare Diseases Database
- EHR: Electronic Health Record
- MDS: Minimum Data Set
- RaDiCo: Rare Disease Cohorts
- SNIIRAM: Information system of the Health Care Insurance
- PMSI: Activity based Payment Information System
- SAE: Hospitals Annual Statistics
- DRESS: Direction for research, studies, evaluation and statistics of the Ministry of Health
- INSEE: National Institute for statistics and economic studies

**Additional Information**

- BNDMR: Banque Nationale de Données Maladies Rares
- bndmr.fr
Flow & data exchanges

- Current situation:
  - One to many databases per RD center of expertise
  - With various applications: paper, Excel file, patient record, local, national or international registries

- Means:
  - The BNDMR team publishes formats for data exchange enabling to communicate with the BNDMR.
  - And accompanies the reference centers in implementing the connectors
  - Security topics concerning patients’ data are discussed with the technical teams.
Sustainability

Sustainability is the capacity to endure.

- Define:
  - Data to collect, common and specific data elements, e-CRF, data entry
  - Data standards
  - Biospecimen
  - Datamonitoring and datamanagement
  - Patients participation

- Define the budget and consider mechanisms for sustainability
- Define ownership.
Data considerations

- What different categories of data are needed from what sources? Professionals, patients themselves.
- What CDEs’ or metadata are needed?
- What are the key quality control issues to tackle?
- What kind of new challenges and opportunities due to «omics» or «Big data» issues?
- How to make useful research data maximally available?
A methodology for a minimum data set for rare diseases to support national centers of excellence for healthcare and research

Rémy Choquet¹,², Meriem Maaroufi¹,², Albane de Carrara¹, Claude Messiha¹, Emmanuel Luigi³, Paul Landais¹,⁴

J Am Med Inform Assoc 2015; 22:76-85

★ EDITOR'S CHOICE ★
Patient reporting outcomes

- Patients provide information about experiences, outcomes, or quality of life.
- It is a voluntary option, opt-in
- It is complementary to clinicians or health professionals reported data
Using standards of transcoding

- Choose the standards to transcode the information in order to increasing *interoperability*
- Standardisation: use standards to discard artifacts (data elements, or information models) and qualify content (coding items)
- Standards for information models/data elements:
  - SNOMED (3.5, CT), HL7, openEHR
- Terminologies:
  - Clinical Terms: LOINC, SNOMED CT
  - Orphan drugs: RxNorm, ATC, Orphanet
  - RD Diagnosis: Orphanet
  - Signs: HPO (ICD10, signs to be validated)
  - Genes: OMIM, Ensembl
CDIDSC & HL7

Two forums for clinical research data standards:

- the Clinical Data Standards Interchange Consortium (CDISC)

- the Regulated Clinical Research (RCRIM) Technical Committee of Health Level Seven (HL7). HL7 version 3 relies upon a very abstract information model: the Reference Information Model (RIM). It is broad and flexible enough to address any messaging need in the healthcare domain.

Richesson RL, Krischer J J Am Med Inform Assoc 2007;14:687-696
Biorepository and Biospecimen

- Establish national rare disease biospecimen repositories using patient registries as sources for donors to build tissue repositories and managing some aspects of informed consent
- Contribute to the Specimen Resource locator
- Improve the issues related to the communication of results of specimen-based research to donors

Data monitoring

- Monitoring the progress of the data entries/research
- Ensure that its conduct and data collection are carried out in accordance with the protocol, the good clinical practices and the regulatory provisions in force for operating procedures.
- Preliminary step of the data quality management.
Data management

- Activity of clinical research that contributes to the documentation and the quality of the database that contains the information collected during the study.

- Uses a variety of methods, tools and processes to ensure that the data are identified, qualified, validated, stored and protected. They thus become reliable, accessible, usable for analyses, and moreover exchangeable.
Select a platform

• Numerous platforms available, including (but not limited to):
  – Patient Crossroads CONNECT
  – Reg4All (Genetic Alliance)
  – PatientsLikeMe
  – CoRDS Registry
  – The Informatics Marketplace (TIMe) (Remedy Informatics)
  – ORDR/GRDR and NORD patient registry and natural history resources \textit{(forthcoming)}
  – Custom-designed platforms

• Consider the strengths, limitations, and costs associated with each

Source: \url{www.globalgenes.org/webinars}
Financing and ownership

- Financing
- Foster public-private partnership
- Ownership according to the law in force in each country
Financing and ownership

• Define a budget for registry design, implementation, and maintenance

• Explore funding mechanisms
  – Grants (private, government)
  – Donors, fundraising
  – Crowd-sourcing
  – Partnering with BioPharma and/or academia
  – Fees for access to registry data

• Look for a long-term funding stream to maintain the registry and maximize the investments

Source: www.globalgenes.org/webinars
GRDR Pilot overview (1)

– New Patient Registries + Existing Registries (Registries retain ownership & control of data)
– Collect And Aggregate Patients Data From Multiple Registries In A Standardized Manner
– Share De-identified Patient Data
– Ability To Conduct Across-Disease Analyses And Recruitment
– Develop And Use Additional Rare Disease Common Data Elements (CDE)
– Utilize A Global Unique Identifier (GUID) to Link Patient Data with Bio-Specimen Samples

Source: SC Croft & Y Rubinstein
GRDR Pilot overview (2)

– Explore Integration Of Electronic Health Records Into GRDR

– Evaluate Data Mapping, Data Export/Import Processes, And Data Mining Capabilities

– Develop An Accessible Web/Open Source Software-based Patient Registry Template

– Collaborations With NIH Institutes and Centers and Patient Advocacy Groups To Develop Disease -Specific standard questions and CDEs

– Developing Data Contribution And Data Access Agreements

Source: SC Croft & Y Rubinstein
joint declaration

• Patients registries (PR): a priority for RD
• RD PR should encompass a wide geographical scope
• Oriented towards a disease/condition rather than a therapeutic intervention
• Define a set of common data elements
• Consider registering patients reported outcomes
• Foster interoperability and harmonization between RD PRs
• Link RD PR with biobanks
• Improve the sustainability, encourage public-private partnership
• Involve patients in the governance
• RD PR a tool for setting up and empowering patients communities