II INTERNATIONAL SUMMER SCHOOL

Rare disease and orphan drug registries

Day 4
18.09.2014

Quality assurance

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Firsts concepts

- **Background**
  - European actions in the field of RD registries
  - Other international actions in the field of RD registries
  - Some projects
    - RD-CONNECT; EPIRARE; IRDiRC registries WG
- **Introduction**
  - Purposes
  - Methods
- **RD registries information**
  - Literature review
  - Orphanet information
  - EPIRARE survey: Quality analysis
- **Terminology and RD registry specificities**
  - Registry definition
  - Quality concepts
  - Quality and Health Care Systems
  - Quality and Research
  - Internal and external validity

Firsts concepts

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International RD Registries projects

IRDiRC
INTERNATIONAL RARE DISEASES RESEARCH CONSORTIUM

RD-CONNECT

RARE DISEASE CONNECT (RD-Connect)

RD-Connect is an integrated platform connecting databases, registries, biobanks and clinical bioinformatics for rare disease research.

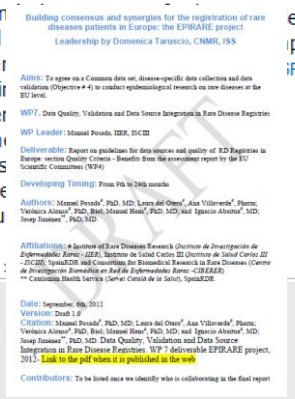
Visit RD-Connect >

EPIRARE

EUROPEAN PLATFORM FOR RARE DISEASES REGISTRIES (EPIRARE)

The aim of EpiRare is to prepare a European platform for the registration of rare disease patients and to ensure the quality an registered researcher experts i assessmer managem build cons to ensure term su platform.

Visit EPIRARE

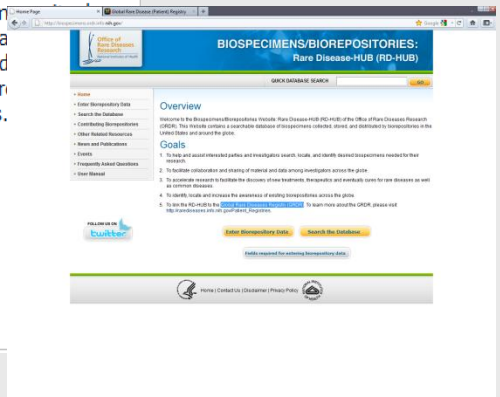


Global Rare Disease Registry

GLOBAL RARE DISEASE REGISTRY (GRDR)

GRDR provides a resource to the rare disease com collecting the pa information need erate resear peutic advances.

iRDR >



Firsts concepts

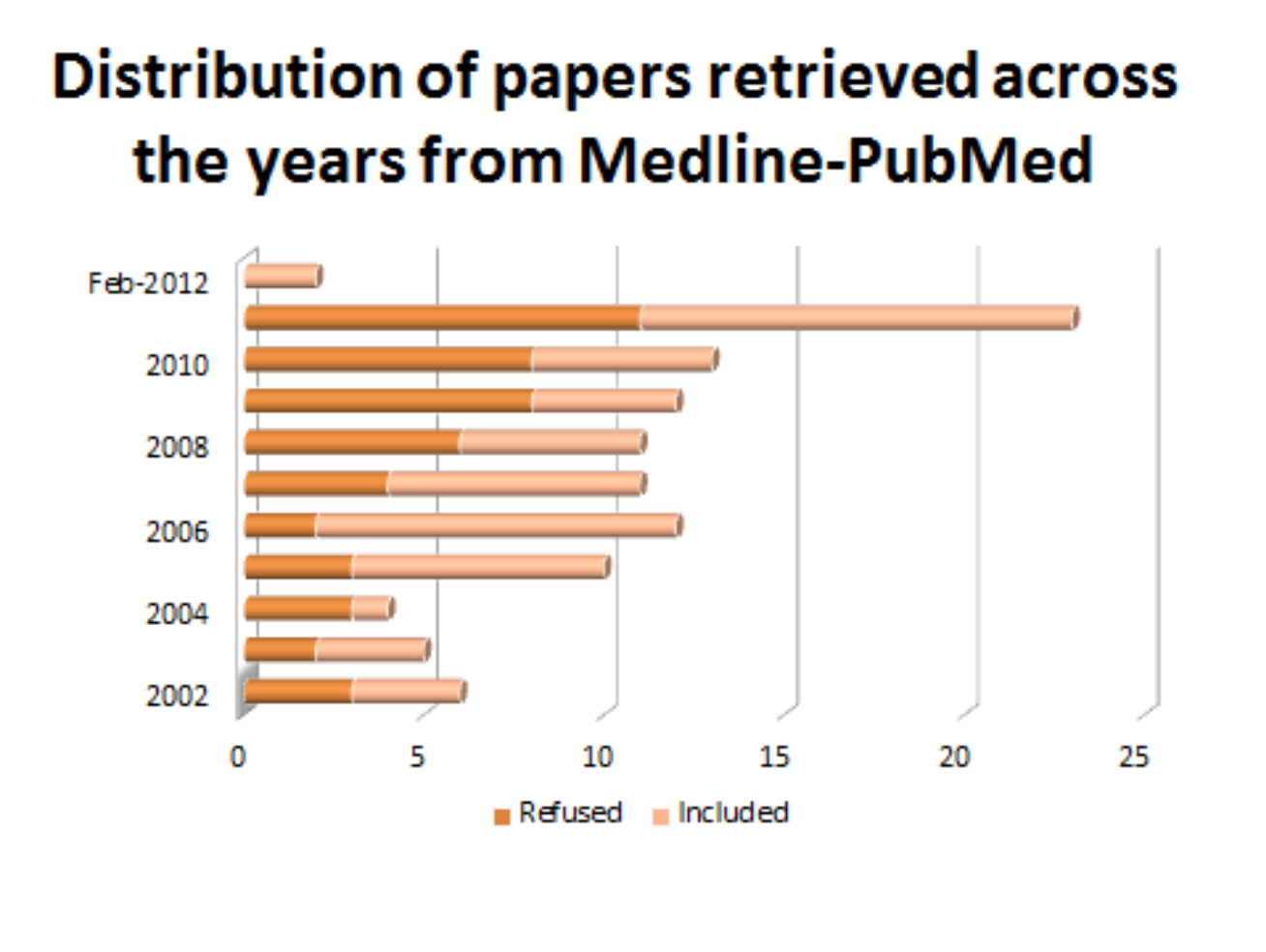
- Purposes
  - To ensure background knowledge in the area of data quality and validity in RD-registering activities, as fundamental criteria for further development RD-registries.
- Methods
  - Literature review
  - Personal and external expertise
  - Stakeholders opinions
  - High level reports and websites

Literature Review

Type of location	Coverage
Electronic database	Medline (PubMed)
General search engines	Google As well as using the general search terms, we also searched for relevant organisations, including patients and professional associations
Specific professional organisations	National health technological assessment agency websites
Councils and committees	European Union Committee of Experts on Rare Diseases (EUCERD); Rare Disease Task Force (RDTF); IIER Ethics Committee; EPPOSI; California HealthCare Foundation
Specific sites	www.iso.org; Centre for Review and Dissemination http://www.crd.york.ac.uk/crdweb/

Literature Review

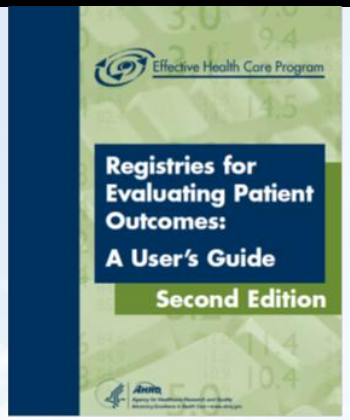
Searching control, quality ; data quality ; validity and reliability validity epidemiology AND registry

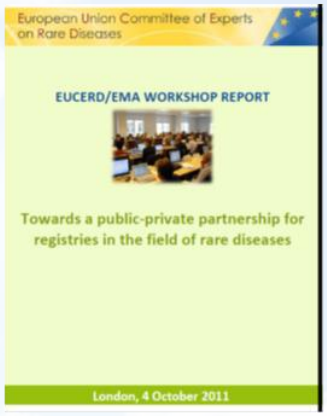


Reports

- **Richesson R and Vehik K**. 2010. Patient registries: Utility, validity and inference. Adv Exp Med Biol. 686: 87-104.
- **DEcIDE Center** . Registry of Patient Registries (RoPR). Policies and Procedures. Version 4.0. Task Order No. 7. Contract No. HHSA290200500351. Prepared by: DEcIDE Center. Draft Submitted September 2, 2011. Available at:http://www.effectivehealthcare.ahrq.gov/ehc/products/311/777/RoPR_PoliciesProcedures_Draft-Report_20110909.pdf
- **RDTF, 2011** Patient registries in the Field of rare diseases. Overview of the issues surrounding the establishment, management, governance and financing of academic registries. Report on patient registries in the field of rare diseases Update June 2011. Available at:http://www.eucerd.eu/upload/file/RDTFRegistriesrev2011.pdf
- **Gliklich RE, Dreyer NA**, eds. 2010. Registries for Evaluating Patient Outcomes: A User's Guide. 2nd ed. (Prepared by Outcome DEcIDE Center [Outcome Sciences, Inc. d/b/a Outcome] under Contract No. HHSA29020050035I TO3.) AHRQ Publication No.10-EHC049. Rockville, MD: Agency for Healthcare Research and Quality. September
- **Peter Wrobel and EPPOSI**. Need for Data Collection to Increase Knowledge on Rare Disorders and Optimize Disease Management and Care. WORKSHOP ON RARE DISEASES REGISTRIES
- **PATIENTS' REGISTRIES FOR RARE DISORDERS**. 18-19 March 2009 FPS Employment, Labour and Social Dialogue Brussels, Belgium
- **Specialised Healthcare Alliance**. Registries Guide 2011. http://www.shca.info
- **EUCERD/EMA WORKSHOP REPORT**. Towards a public-private partnership for registries in the field of rare diseases. http://www.eucerd.eu/upload/file/Meeting/EUCERD/EUCERDWorkshopRegistries2011.pdf
- **Guide on Methodological Standards in Pharmacoepidemiology** (Revision 1) EMA/95098/2010 Page 31/44 (amended) 11 July 2012 http://www.encepp.eu/standards_and_guidances/index.html
- **Ulmer C, Bruno M, Burke S**, eds. Future directions for the National Healthcare Quality and Disparities Reports. Committee on Future Directions of the National Healthcare Quality and Disparities Reports, Institute of Medicine. Washington, DC: National Academies Press; 2010. ww.ahrq.gov/qual/qrdr10.htm
- **U.S. Department of Health and Human Services**. Agency for Healthcare Research and Quality. National Healthcare Quality Report AHRQ Publication No. 11-0004. March 2011. www.ahrq.gov/qual/qrdr10.htm

Reports and papers






Clinical Epidemiology

Dovepress

ORIGINAL RESEARCH

Challenges in validating quality of care data in a schizophrenia registry: experience from the Danish National Indicator Project

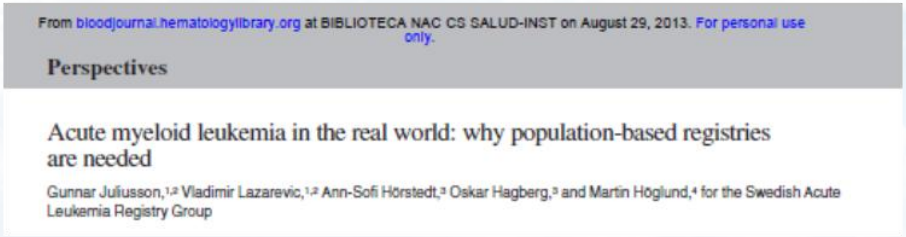
This article was published in the following Dove Press journal:
Clinical Epidemiology
9 August 2012
Number of times this article has been viewed


Clinical Epidemiology

Dovepress

ORIGINAL RESEARCH

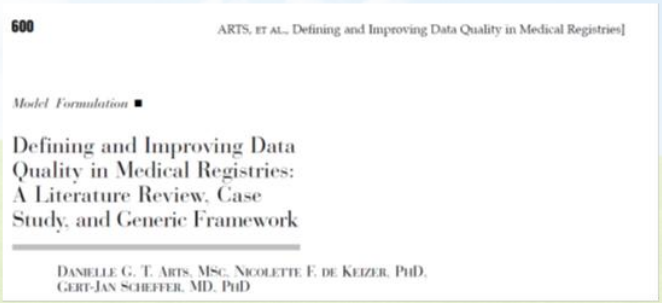
Registration in the Danish Regional Nonmelanoma Skin Cancer Dermatology Database: completeness of registration and accuracy of key variables



Perspectives

Acute myeloid leukemia in the real world: why population-based registries are needed

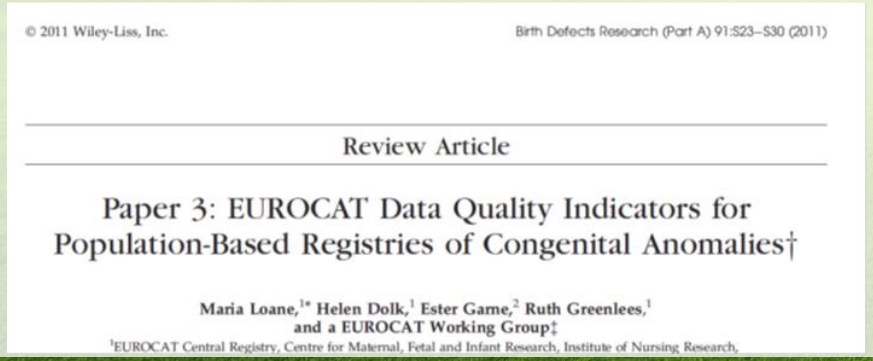
Gunnar Juliusson,[1,2] Vladimir Lazarevic,[1,2] Ann-Sofi Hörstedt,[3] Oskar Hagberg,[3] and Martin Höglund,[4] for the Swedish Acute Leukemia Registry Group


600 ARTS, ET AL., Defining and Improving Data Quality in Medical Registries]

Model Formulation ■

Defining and Improving Data Quality in Medical Registries: A Literature Review, Case Study, and Generic Framework

DANIELLE G. T. ARTS, MSC, NICOLETTE F. DE KEIZER, PHD, GERT-JAN SCHEFFER, MD, PHD



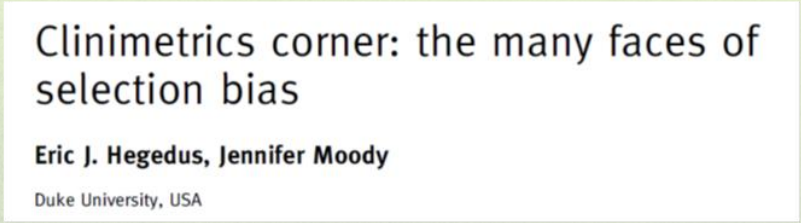
Birth Defects Research (Part A) 91:S23–S30 (2011)

Review Article

Paper 3: EUROCAT Data Quality Indicators for Population-Based Registries of Congenital Anomalies†

Maria Loane,[1]* Helen Dolk,[1] Ester Garne,[2] Ruth Greenlees,[1] and a EUROCAT Working Group‡

[1]EUROCAT Central Registry, Centre for Maternal, Fetal and Infant Research, Institute of Nursing Research,

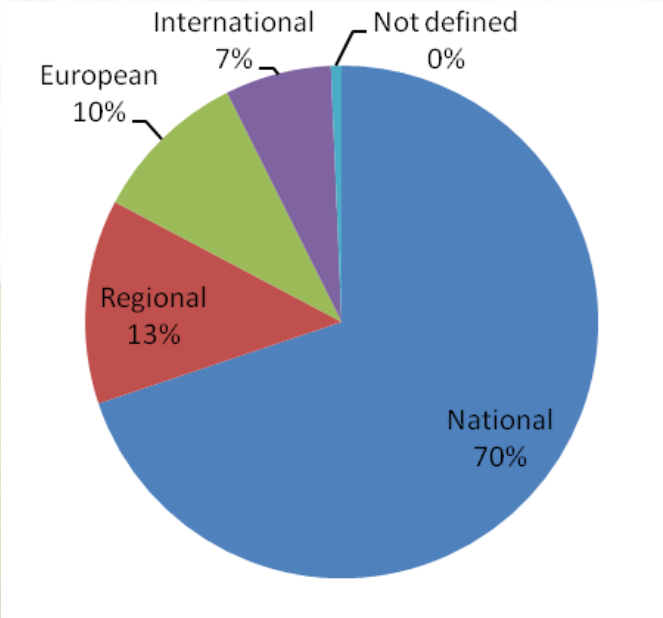

Clinimetrics corner: the many faces of selection bias

Eric J. Hegedus, Jennifer Moody

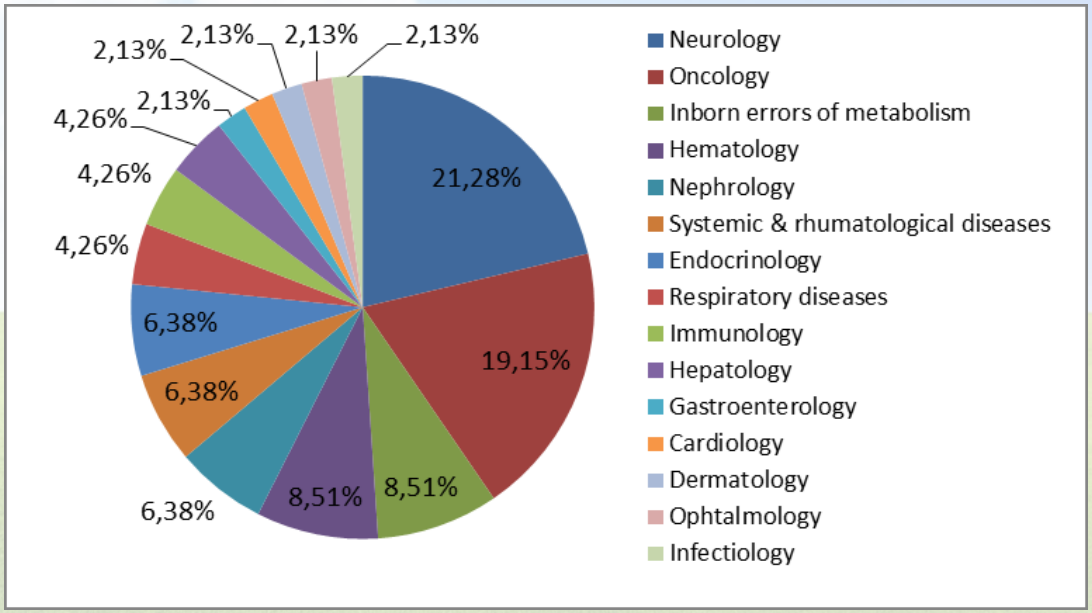
Duke University, USA

Orphanet report

Geographical coverage of rare disease registries, 2012



Medical areas with patient registries, 2011



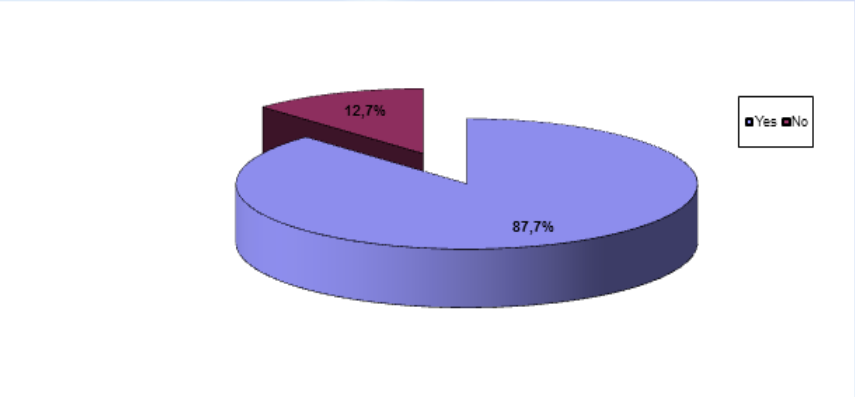
EPIRARE survey and quality registries

Survey on RDR Quality-I

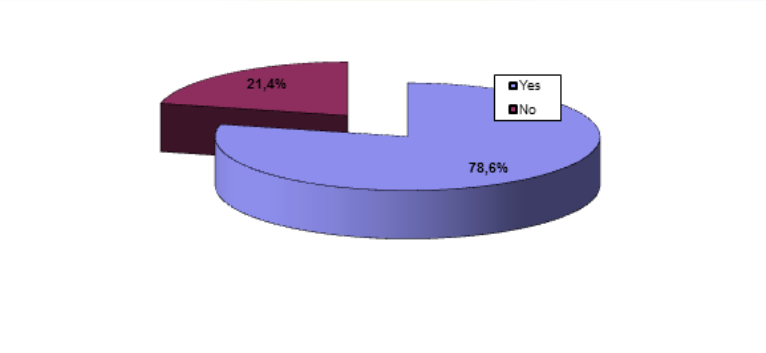
- GENERAL CHARACTERISTICS OF THE REGISTER (5 questions)
- AIMS AND SCOPE OF THE REGISTER (4 questions)
- COLLECTED DATA (6 questions)
- REGISTER´S SOURCES (3 questions)
- QUALITY OF DATA (9 questions)
- ETHICAL AND LEGAL ISSUES (4 questions)
- INFORMED CONSENT (4 questions)
- GOVERNANCE (2 questions)
- COMMUNICATION (2 questions)
- ACCESS TO DATA AND SECURITY (6 questions)
- REGISTER`S SUSTAINABILITY (5 questions)
- NEEDS AND EXPECTATIONS (6 questions)

Case definition
Inclusion/exclusion criteria

- **Q0013 Case definition available for the RD of interest (87,7%)**



- **Q0014 Standardised inclusion/exclusion criteria (78,6%)**



Quality Assessment

- **Q0025 Registry checked for reliability (48,6%)**
- **Q0026 Registry checked for agreement (46,4%)**
- **Q0027 Registry checked for internal validity (58,2%)**
- **Q0028 Quality test/surveys periodically performed (43,6%)**
- **Q0029 Methods to avoid duplication of the registered cases (87,7%)**

Survey Summary

- **The quality of survey was high**
- **Good level of quality among RDR participants in that survey**
  - **Case definition; inclusion/exclusion Criteria Data are periodically updated**
  - **Standardized data entry processes**
  - **Control of mistakes**
  - **Instructions and training**

Registry Definition and Procedures

What is a registry?

- Organized information system
- Observational study design
- Collect uniform data
- Evaluate specified outcomes
- Population defined
- Predetermined purposes
  - Scientific
  - Clinical
  - Policy

Registry vs database

Quality terminology

- The term "**quality**" refers to the degree of excellence, as in, "a quality product". Yet, one could also define this term as ***fitness for the purpose***
- **Other terms related/surnames**
  - **Quality Assurance (QA)**
  - **Quality Control (QC)**
  - **Quality Indicators (QInd)**
  - **Quality Assessment (QAss)**
  - **Quality Results (QR)**
- **Quality and Health Care Systems**

Defining a quality assessment framework

Data quality
Features and characteristics of a data set, that bear on its ability to satisfy the needs that result from the intended use of the data.

Quality Assurance (QA)
Activities undertaken before data collection to ensure that the data are of the highest possible quality at the time of collection

Quality Control (QC)
Activities undertaken during and after data collection aimed at identifying and correcting sources of data errors

Quality Assessment (Qass)
Process of quality evaluation of the consolidated database

Quality Results (QR)
Value or set of values resulting from applying a data quality measures

Quality Indicators (QInd)
List of quality measurements

Health Care Quality Scheme

Crosscutting Dimensions	Components of Quality Care	Types of Care		
		Preventive Care	Acute Treatment	Chronic Condition Management
EQUITY / VALUE	Effectiveness			
	Safety Timeliness			
	Patient/Family Centeredness			
	Access			
	Efficiency			
	Care Coordination			
	Health Systems Infrastructure Capabilities			

Source: Ulmer C, Bruno M, Burke S, eds. Future directions for the National Healthcare Quality and Disparities Reports. Committee on Future Directions of the National Healthcare Quality and Disparities Reports, Institute of Medicine. Washington, DC: National Academies Press; 2010.

RD registry procedures

- Study aims and hypothesis with their background and bases
- Definition of the target population, settings and study population
- Study design
- Case definition and inclusion/exclusion criteria
- List of set of variables including sources and definitions
- Standardized data report form
- Pilot study phase description (not always is needed)
- Data collection methods
- Data interpretation/abstraction
- Data codification
- Data stored
- Data analysis
- Ethical issues
- Study limitations and bias analysis
- Standardized data reporting, including discussion of results and their relationships with other published studies

Quality RDR Topics

Main Topics

- Case ascertainment
- Standardized data report form (DRF)
- Data collection
- Results
- Global assesment
- Reporting
- Translation
- Research
- Data delivery and ethical issues
- Patient involvement

RD registry tasks involving quality assurance
Design phase

- Background and fundamental bases of the registry
- General and specific aims
- Geographical and long-term settings
- Target and study populations
- Design
- Case-definition
- Case-inclusion and -exclusion criteria
- Sources of cases
- List of co-variables
- Data model and data dictionary
- Identification of disease codes and co-variables codification
- Statistical analysis plan

- Operating manual including standardized procedures and report forms
- Training
- Pilot testing
- Data collection
- Data stored, access and safety
- Data delivery
- Quality control procedures
- Reporting
- External assessment
- Governance
- Patient involvement
- Long-term funding
- Ethical and legal issues

Key Points

- Inclusion/exclusion criteria
  (use of case definitions, definition of conditions to admit
  disease- or treatment-specific data)

- Coding and classification

- Monitoring of data collection procedures

Types of errors

1) Problems in case selection and case ascertainment; duplicates, mistakes in the interpretation and diagnosis

2) errors in coding, data entry, data transformation, accuracy

3) Data consistency across sites and over time

4) Intentional errors.

Quality & Research

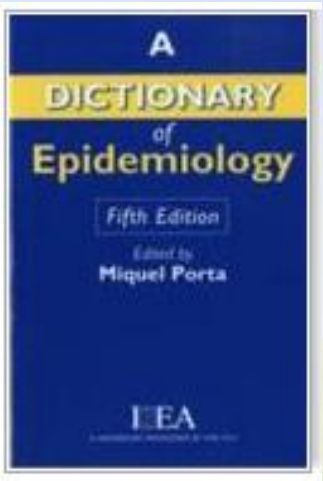
- **Internal validity**
- **External validity**
  - ***Consistency***
  - ***Coherence***
- **Intramethod reliability**
  - ***Test–retest reliability***
  - ***Interrater reliability***
- **Intermethod reliability**

Reliability

The degree of stability exhibited when a measurement is repeated under identical conditions

It refers to the degree to which the results obtained by a measurement procedure can be repeated.

Lack of reliability may arise from divergences between observers or instruments of measurement or instability of the attribute being measured

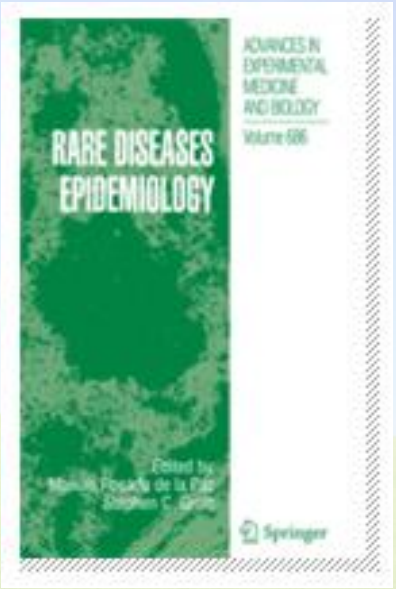


M. Porta. A dictionary of epidemiology. 5th Ed. Oxford University Press (2008)

Sensitivity

- Probability that a subject who is truly diseased will be classified as such by the method used for ascertainment

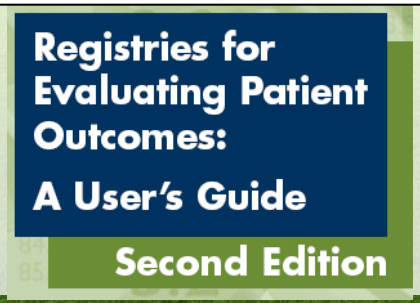
- Estimates how successful a registry is at identifying all the events, cases or exposures in the target population



Internal Validity

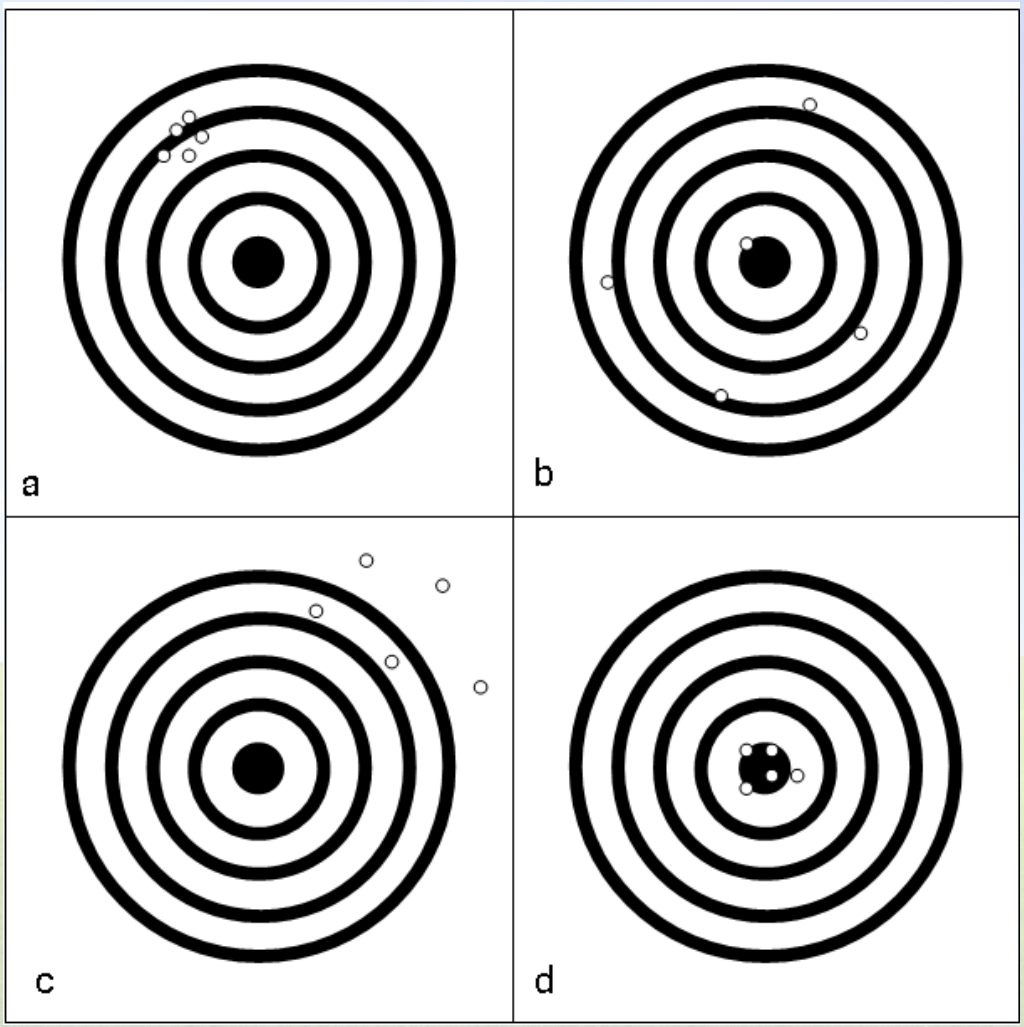
"The extent to which study results are free from bias, and the reported association between exposure and outcome is not due to unmeasured or uncontrolled-for variables" (AQHRQ 2010)

- Depends on methods used to select the subjects and collect information
- Internal validity is a *prerequisite* for external validity



Types of Bias

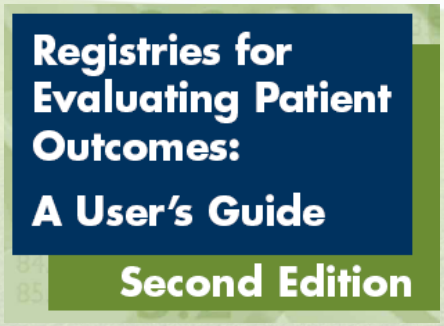
a – high precision (low variance) but biased;
b – low precision (high variance) but no overall bias;
c – low precision (high variance) and biased;
d – high precision (low variance) and no bias



External validity (Generalization)

- It refers to the utility of the inferences for the broader population that the study subjects are intended to represent.

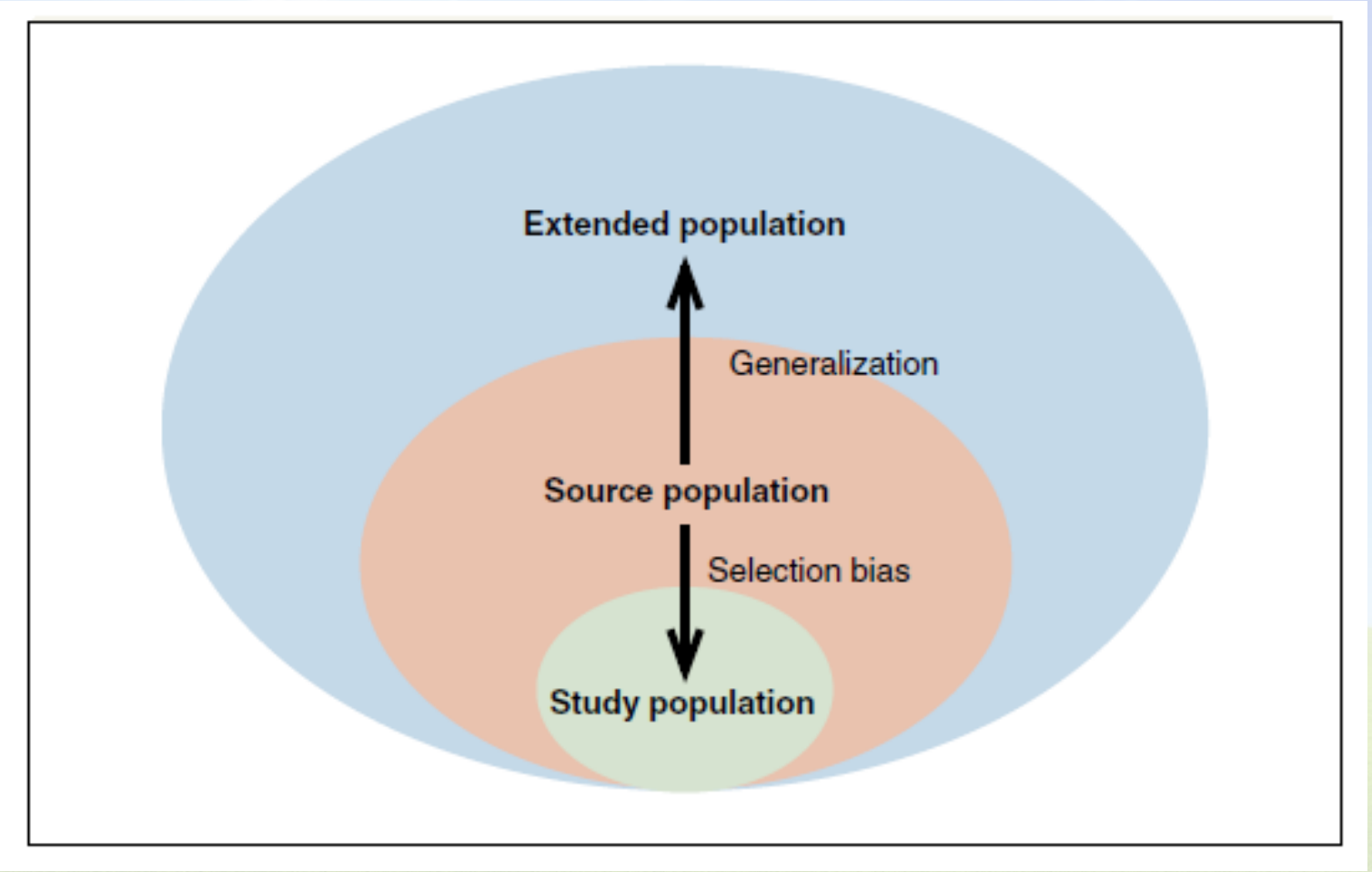
- The way in which patients are recruited, classified, and followed can either enhance or diminish the external validity of a registry. (AQHRQ 2010)



Internal Validity Assessment

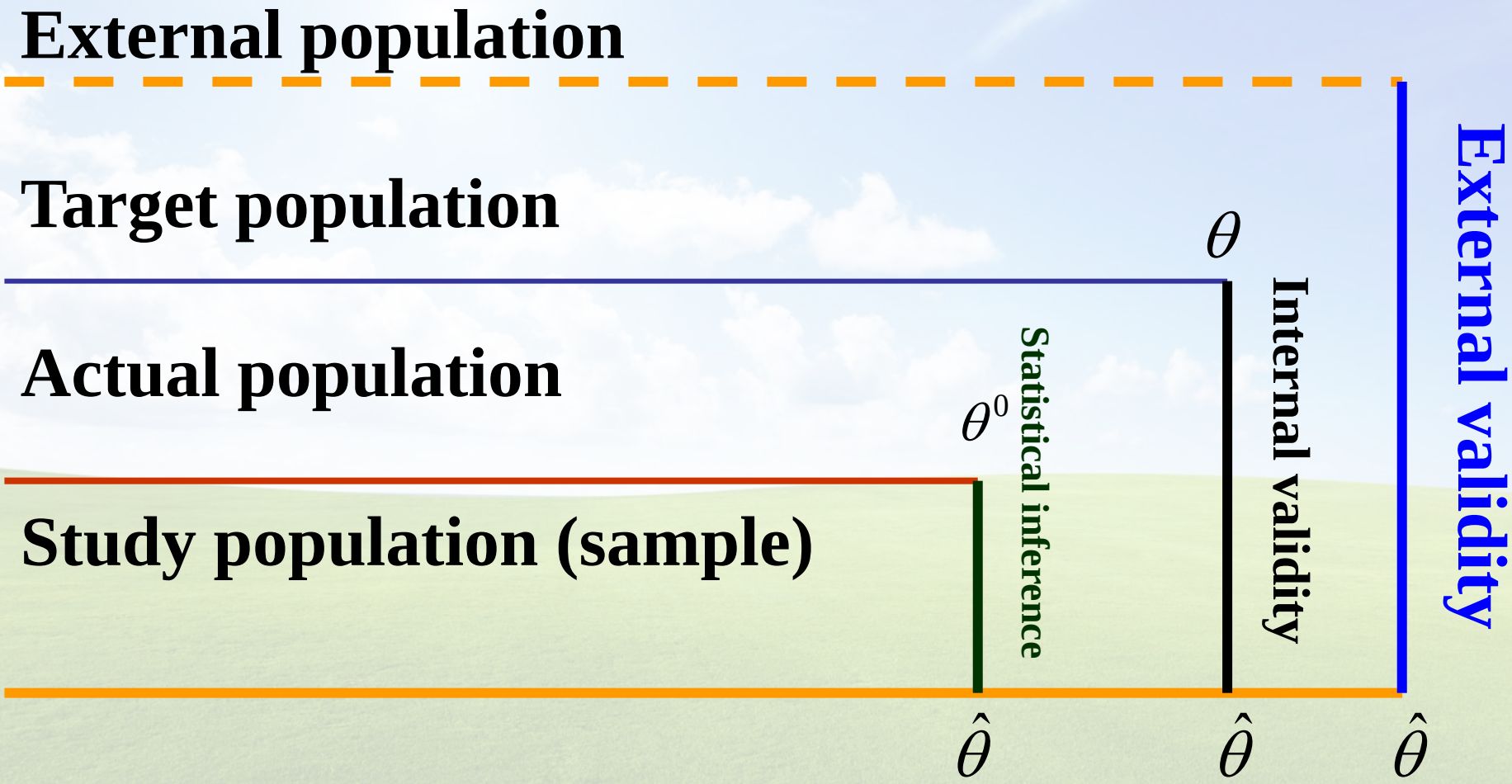
- Study aims and hypothesis with their background and bases
- Definition of the target population, settings and study population
- Study design
- Case definition and inclusion/exclusion criteria
- List of set of variables including sources and definitions
- Standardized data report form
- Pilot study phase description (not always is needed)
- Data collection methods
- Data interpretation/abstraction
- Data codification
- Data stored
- Data analysis
- Ethical issues
- Study limitations and bias analysis
- Standardized data reporting, including discussion of results and their relationships with other published studies

General Scheme



Study population: subjects included in the study's final analysis.
Source population: population from which the study population originated.

Types of Validity



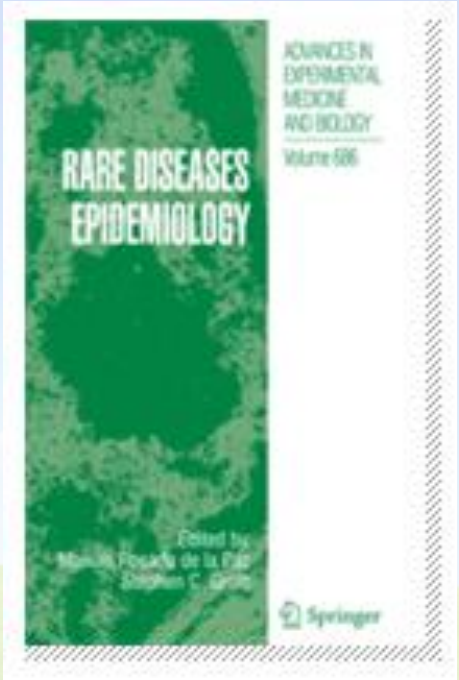
Quality & Research

- Internal validity
- **External validity**
  - ***Consistency***
  - ***Coherence***
- Intramethod reliability
  - *Test–retest reliability*
  - *Interrater reliability*
- Intermethod reliability

Completeness of case ascertainment

The inclusion of all cases in the sample area time or place

- Essential to determine the accuracy of the true incidence or prevalence of a RD in the population
- Conclusions
- Extrapolations to the general population



Richesson R, Vehik K. Patient registries: utility, validity and inference. Adv Exp Med Biol 2010;686:87-104.

Outcomes Publishing

- **STROBE** - Strengthening the Reporting of Observational Studies in Epidemiology
- **STROBE-ME** - STrengthening the Reporting of OBservational studies in Epidemiology
- **STREGA** - STrengthening the REporting of Genetic Association Studies
- **GRIPS** - Strengthening the reporting of genetic risk prediction studies
- **CONSORT**- Consolidated Standards of Reporting Trials
- **PRISMA** - Preferred Reporting Items for Systematic Reviews and Meta-Analyses
- **MOOSE** - Meta-analysis Of Observational Studies in Epidemiology
- **STARD** - Standards for Reporting of Diagnostic Accuracy
- **REMARK**- REporting recommendations for tumor MARKer prognostic studies
- **GRACE -** Good Research for Comparative Effectiveness
- **GRRAS** - Guidelines for Reporting Reliability and Agreement Studies

Quality Assurance Plan

GUIDELINES FOR QUALITY OF RD REGISTRIES

- **Addressing systematisation of quality procedures**
- **The development of a quality assurance plan**
  - Quality control measures
  - Data security and confidentiality
  - Follow-up
  - Timeliness
  - Reporting
  - Coordination
- **Manual of Procedures**

- *Policy rules and governance*
- *IT tools document*
- Security document
- *Ethic rules*
- *List of procedures for each topic*
- *Manual training*
- *Instructions for database users*

- *Data dictionary*
- *Data Report Form*
- *Catalogues*
- *Classifications*
- *Personnel functions and tasks*
- *Checklists*
- *Nested research study protocols*
- *Quality assessment*

Assessment Phase

- **The development of a quality assurance plan**
- **Quality control measures**
  - ***Data security and confidentiality***
  - ***follow-up***
  - ***timeliness***
- ***Reporting***
- ***Coordination***
- **Quality Indicators**
- **External assessment**

Quality Indicators

- **Provide assessment of quality and disparity**
- **Provide baselines to track progresses**
- **Identify information gaps**
- **Emphasize interdependence of quality and disparities**
- **Promote awareness and changes of the not so well procedures**

Quality Indicators

- *Surveillance of RD registry activities*
- *Case ascertainment*
- *Analysis of data completeness*
  - data collection system
  - access to necessary source documents
  - item abstraction process
  - coding rules
  - rate of diagnostic case verification
  - rate of duplicate cases detected
  - relationship between mortality cases detected in the national index of death and case already registered
- *Consistency*
- *Timelines*
- *Data security and confidentiality*
- *Validity*

Outcomes Quality

- **Indicators**
  - **Process indicators**
  - **Monitoring indicators**
  - **Outcome indicators**
- **Quality assurance (user satisfaction assessment) of tools and services, including promotion of registration and networking**
  - **Identify improvement opportunities.**
  - **Tools and Resources Quality**

QUALITY ASSURANCE PLAN FOR RARE DISEASES REGISTRIES AND DATABASES PLATFORM

QAP: European Platform

- **RD registry's QAP *vs* RDR platform's QAP**
  - Registry Description, Sponsor and Conditions of Access, Registry Design, Eligibility for enrollment, Common Data Element Groups, Manuals of procedures, Progress Report could vary in the size but not in the general principles, which are essentially the same
  - Use of a indicators checklist is also similar although whit different scopes
  - Fulfill the requirements and stakeholders needs are common aims either a registry or a RDR platform
  - Governance process and ethical issues involve much more complexity
  - Management IT tools system is also more complete and complicated because it is necessary to add procedures for each one of their components
  - The development of SOP show also a high level of complexity because they should define the relationships among several type of stakeholders and aims
  - A problems solution system and mechanisms for making decisions should be also implemented but aimed to supra aims instead specific aims, which are addressed in a registry.

QAP: European Platform

- About type of data
  - Metadata of each RD registry
  - Aggregated information data
  - De-identify data
- About type of providers
  - Registries owner
  - European Reference Network scheme
  - National partners
- About outcomes an outputs
  - As source of epidemiological information on RD (including natural history of RD)
  - As source of patients for research studies
  - As source of surveillance for side drug effects, cost-effectiveness analysis, etc

QAP: European Platform

- **Description:** identification and description information
- **Classification and Purpose:** information about the type of registry and its intended purpose
- **Governance:** holders as well as some external experts should be involved
- **Sponsor:** information about the sponsor, collaborators
- **Conditions of Access and related contact information**
- **Ownership:** The platform should recognize the ownership of the achievements reached by the participating registries
- **Design:** information and references to the Registry design, including the protocol definition
- **Eligibility:** criteria for patient enrollment in the registry.
- **Common Data Elements**
- **Quality Procedures:** information about the quality procedures being conducted for the registry
- **Progress Report:** information associated with the registry including growth of the registry and any relevant references to available progress reports.
- **Other related Information:** links to related publications, citations, and other relevant information

QAP: European Platform

- **Governance and Quality**
  - **Registry platform Holders, who would provide information regarding their registries.**
  - **Registry platform Users, who would search and find information regarding registries included in the platform**
  - **Registry Platform Reviewers, who would ensure the listed registry information was accurate, consistent, and of high quality**
  - **Registry Platform Administrators, who would handle the maintenance and operation of the platform, and support the needs of the preceding roles**

- **Coordinating mechanisms**
  - **import data from patient registries and databases using the Common Data Elements previously agreed**
  - **use the collected information to find subsets of patients who may be potential candidates to participate either clinical trial or observational studies.**
  - **participating registries will retain their data ownership and control and they may collect additional data beyond the CDEs core**
  - **researchers can also use the information to report about the latest research findings to those families already registered**
- **Ethics and Quality**

QAP: European Platform

- **Manual of Procedures**
- **Data quality**
  - **Common Data Elements (CDEs) and their definitions in a standardized and meaningful manner**
  - **should determine which Data Elements are absolutely necessary and which are desirable but not essential.**
  - **should develop a guide of use of CDE to give indications of how to handle definition and other coding problems or inclusion criteria**
  - **would define a general training manual**
  - **would carry out general staff training sessions**
  - **should establish an internal and external assessments (analysis) of quality**
  - **validity of data and perform periodic data quality reports**
  - **could develop a quality data criteria checklist to help in the quality data assessment**

SainRDR: The Spanish RDR experience and Quality Issues adopted

Patient unique identifier

Thank you

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