21. The European Cystic Fibrosis Registry

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1. INTRODUCTION

- Patient registries are large databases containing systematic, standardized and anonymized health data from patients with mostly rare diseases. Such supra-regional data collections are widespread in the medical field these days, as they provide important information from a large number of patients (e.g. on the health status of patients, on the efficacy and safety of therapies or on complications of a distinct disease).
- Registries are superior to local (e.g. centre-based) observations in terms of case numbers and representativeness of the results.
- Consequently, patient registries lead not only to improvements in research progress, but also serve directly patients by continuously enhancing the quality of care and disease management.
- In this frame, annual international data analyses play an important role to a growing number of scientific projects (registry studies).
- The most important tasks of patient registries are shown in **Table 1**.

Table 1. Important tasks of an international patient registry

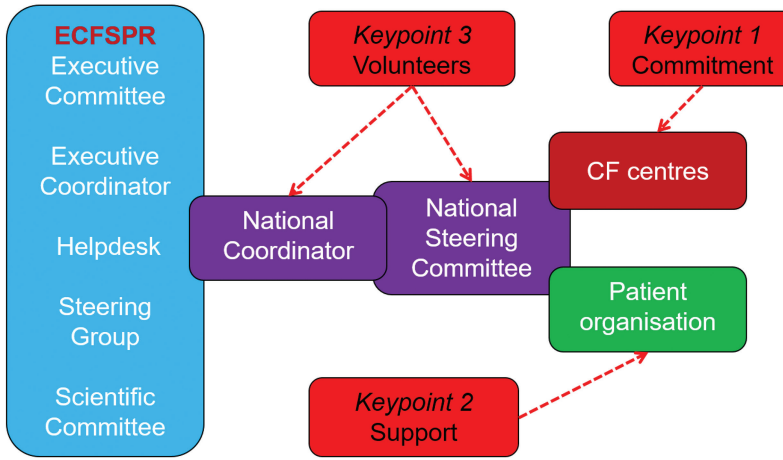
Task	Example
Registry studies	– Description of health status – Identification of disease-modifying factors – Prediction of survival
Benchmarking	– Surveillance of medical care quality – Identification of areas for improvement – Supervision of steps to optimize standards of care
Pharmacovigilance	– Surveillance of drug efficacy and safety – Post-marketing studies – Monitoring of limitations in drug licensing

2. THE EUROPEAN CYSTIC FIBROSIS SOCIETY PATIENT REGISTRY (ECFSPR)

- Switzerland participates in the Patient Registry of the European Cystic Fibrosis Society (ECFS) since 2008. As all Swiss CF centres take part in the registry since 2015, it is expected that from 2018, all Swiss CF patients – except for very few exceptions – are included in the ECFSPR.

- By this, Switzerland not only contributes to European data analyses and registry-based research projects, but Swiss CF centres and researchers are entitled to access and analyse the ECFSPR database via standardized data requests to answer scientific questions and to optimize patient care.
- Written informed consent must be obtained by the CF centres from all patients and/or caregivers before inclusion into the ECFSPR. Upon reaching legal age, patients need to sign the consent form again. The consent includes an agreement to scientific data analyses.
- Data entry of CF-relevant health information on each patient is done by the CF centre at least annually, although encounter-based data entry (for each patient visit, e.g. 3-monthly) is also possible in the registry software (ECFSTracker).
- The definition of each variable is standardized and must be closely followed during data entry. Information for inclusion criteria, data protection, data entry and variables can be found online (see **Infobox**).
- Training on data entry into ECFSTracker is offered regularly by the ECFSPR service desk; for further information the National Coordinator should be contacted.
- For a successful implementation and maintenance of a patient registry, a range of structural and human resources are needed, as shown in **Figure 1**.
  - CF centres, the Swiss Working Group for Cystic Fibrosis (SWGCF) and the Swiss Association for Cystic Fibrosis (CFCH) work together closely to ensure a complete and precise documentation of all Swiss CF patients in the registry.
  - The National Steering Committee (which corresponds to the SWGCF in Switzerland) appoints and sends a National Coordinator into the ECFSPR Steering Group.
  - Further information on the structure of the ECFSPR can be found on the website (see **Infobox**).

Figure 1. Structure of the ECFSPR.



3. DATA QUALITY: CHALLENGES AND SOLUTIONS

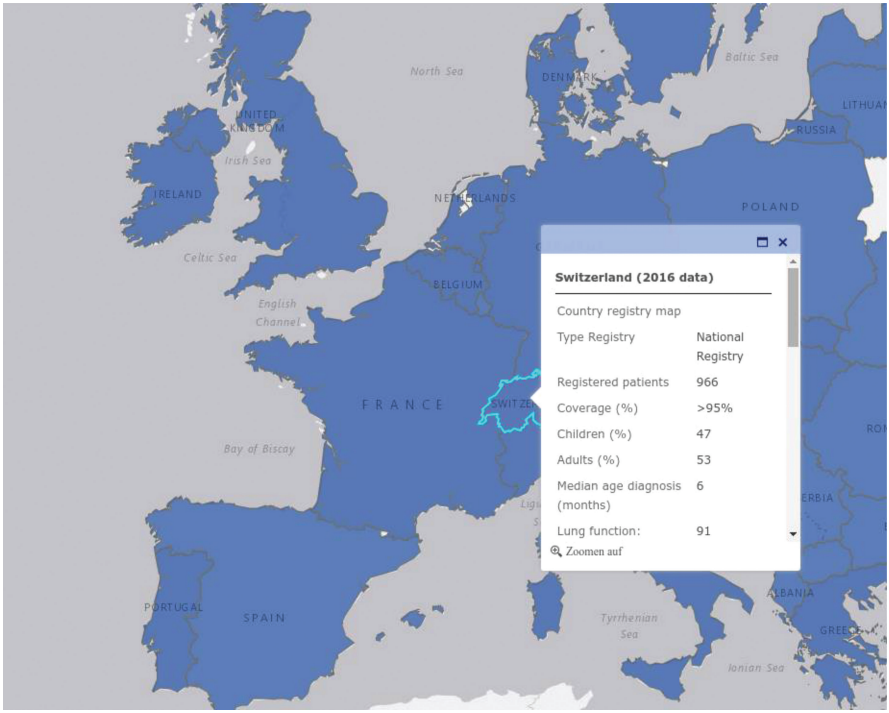
- Informative value, reliability and representativeness of data analyses from a patient registry depends on the quality and completeness of data. Important factors affecting data quality are
  - Incomplete participation of CF centres and patients
  - Incomplete or missing data
  - Incorrect data
  - Wrong application of definitions
  - Missed deadlines for data entry
- The ECFSPR has implemented a range of actions to guarantee optimal data quality and to ensure sustained trust in registry analyses and studies, amongst them
  - Standardized contracts with participating centres
  - Unanimous definitions and descriptions of variables
  - Trainings for CF centres and documentation officers
  - Support of participating centres by a service desk
  - National Coordinators serving as interface between centres and the ECFSPR
  - Centralized data management, plausibility controls and analysis by statisticians
  - Standardized proceedings for benchmarking projects
  - Audits (on-site visits)
  - Working groups dealing with data quality, variable definitions and harmonization of national registries
- In Switzerland, a number of additional measures to improve data quality have been implemented, such as
  - Financial reimbursement by CFCH for data entry
  - Annual verification of data quality by the National Coordinator and feedback to centres
  - Implementation of a nationwide audit process

4. REGISTRY STUDIES

- The ECFSPR provides annual data reports containing a complete descriptive and comparative analysis of all registry data.
  - The reports can be downloaded on the ECFSPR website (see **Info box**).
  - For lay people, a simplified «at-a-glance report» is allocated every year.
  - Additionally, an interactive map depicting the most important registry data for each country is accessible on the website **(Figure 2).**
- While annual reports address mainly the health status of CF patients in Europe and participating countries, targeted registry studies answer important scientific questions on a large international data set (in 2017, more than 44.000 CF patients were registered in the ECFSPR).
- Research groups, CF centres, patient organisations and industry are entitled to fill in data requests to the ECFSPR following a standardized procedure.
- The applications are reviewed by the ECFSPR Scientific Committee and the Steering Committee and, upon positive recommendation, approved by the Executive Committee.
- Projects must fulfil common research criteria, need to contain a clear and innovative scientific question and must not target on marketing analysis.

- Results should be made available to the community in a peer-reviewed journal. A growing list of publications derived from registry studies is available on the ECFSPR website.
- Application forms are provided online (see **Info box**).

Figure 2. Interactive map, accessible on the ECFSPR website, showing important Registry data in a comprehensive manner for each participating country.

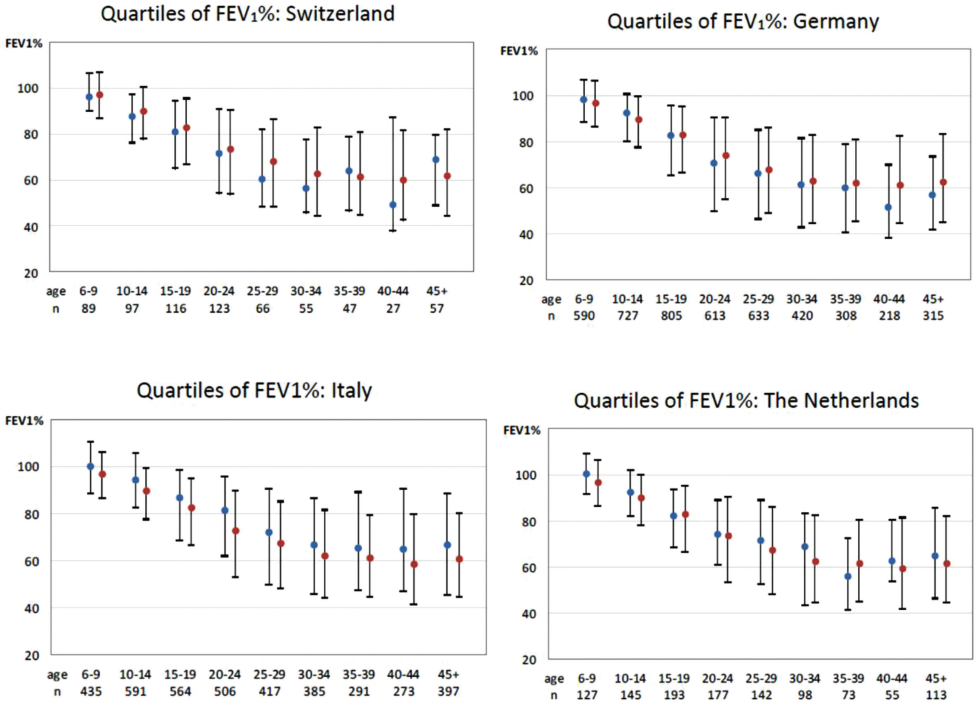


5. BENCHMARKING

- Benchmarking allows to compare indicators of medical care quality (= benchmarks) within a distinct population, e.g. people with CF in a country or between different countries.
- The most important aim of benchmarking is to increase, harmonize and secure quality of medical care in Switzerland and Europe to the highest level achievable.
- For this purpose, data of different centres or countries are compared, areas of improvement are identified, and measures of optimization are implemented.
- In this process, profound analysis of identified differences between centres is crucial, as a number of deviations may not correspond to quality of care, e.g. mean lung function might be lower in centres that take care of a larger number of patients with advanced lung disease.
- As a result, all CF patients and CF centres can equally benefit from a benchmarking project.

- On a European level, a specific benchmarking module is available in ECFSTracker from version 2.0 (2019), allowing direct comparison of centres and countries; as a requirement, all CF centres of a country must have approved this application and must have received training in benchmarking (e.g. by an ECFS online course).
- In Switzerland, SWGCF has implemented a national benchmarking project stating from 2019.
- A simplified visualization of country-specific differences is part of the ECFSPR annual report, as shown exemplary for lung function (FEV_1) for selected countries in **Figure 3**.

Figure 3. Comparison of FEV_1 predicted between Switzerland or other European countries (blue dots) and Europe (red dots), stratified for age groups. Median and quartiles are depicted. ECFSPR Annual Report 2016; Orenti A, Zolin A, Naehrlich L, van Rens J et al., 2018.



6. PHARMACOVIGILANCE

- Pharmacovigilance describes a prospective, continuous and systematic surveillance of the efficacy and safety of licenced drugs in the frame of post-marketing studies.
- In recent years, patient registries have been increasingly used as platforms for pharmacovigilance studies.

- ECFSTracker facilitates implementation of specific variables for any post-marketing study by its modular character. Moreover, rigid standardization and control of data quality necessary for scientific projects is established and guaranteed in the ECFSPR.
- As a result, the European Medical Agency (EMA) has officially accredited the ECFSPR as a platform for post-authorisation safety surveillance (PASS) and efficacy (PAES) studies in 2018.
- An internationally recognised example of registry-based pharmacovigilance in Switzerland is the surveillance of the efficacy of Kalydeco® in the frame of its limited disposal by the Swiss Health Authorities (BAG).
  - According to this, reimbursement of Kalydeco® requires documentation of a defined minimal improvement in lung function or sweat chloride every three months and an annual report issued to the BAG for each individual patient.
  - Additionally, the number and duration of pulmonary exacerbations must be monitored.
  - A specific ECFSTracker module was created for this purpose for all Swiss CF centres.
  - In case a patient does not fulfil the limitation, Kalydeco® must be withdrawn as reimbursement is no longer provided.

7. INFO BOX ECFSPR

- Detailed information on the ECFSPR including interactive map: https://www.ecfs.eu/ecfspr
- List of variables and definitions: https://www.ecfs.eu/projects/ecfs-patient-registry/Variables-Definitions
- Application form for data requests: https://www.ecfs.eu/projects/ecfs-patient-registry/data-request-application
- ECFSPR annual reports and at-a-glance reports: https://www.ecfs.eu/projects/ecfs-patient-registry/annual-reports
- Listing of scientific publications from the ECFSPR: https://www.ecfs.eu/projects/ecfs-patient-registry/articles