Copenhagen Economics

EHC THINK TANK REGISTRY MAPPING

An overview of rare bleeding disorder registries across Europe

European Haemophilia Consortium

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Executive summary (1/2)

Real World Data (RWD) have become an important part of drug development and evaluation. Multi-centre analysis is an opportunity for rare diseases.
It is clear that RWD have become an important part of both the development and the evaluation of new and novel therapies. For rare diseases, the challenge is to identify a sufficient number of patients when performing analyses. One solution that has been put forward is to perform analyses using multiple data sources. The challenge is to set up a governance structure for such analyses.

The first step in defining a governance structure is to map out what registries and data are currently available and evaluate where there are opportunities for development. This report presents the results of the mapping of registries for rare bleeding disorders. The mapping was commissioned by the European Haemophilia Consortium.

Data from 12 countries are included in our analysis.
We mapped 18 registries of rare bleeding disorders. By combining interviews with desk research we identified opportunities for future collaboration and areas of development. We extracted exhaustive information for 12 of the 18 countries. For the remaining six countries, we found no or only very limited information.
We confirmed that at least seven of the registries evaluated collect longitudinal data, i.e., data for the same patient are collected over multiple years. The longitudinal approach to collecting data has enabled multiple peer-reviewed publications from several of the registries. Portugal does not have a registry, but treatment centres report annual cross-sectional data to the Ministry of Health.

There are good data on treatment and bleeding events.
The general way data are being collected is by extracting data from electronic medical charts (EMR). The exception is the Czech Republic, where the data collection is based on clinical report forms (CRF). Ireland collects the data to the registry and then transfers them to the EMR. Data on both minor and major bleeding events are collected from either the medical charts or the CRFs. The EMR and CRFs both collect data on treatment and dosage. We did not identify any missing information regarding treatment in desk research or in the interviews. All registries, apart from Greece, collect data on coinfections and inhibitors. Some of the registries collect data on all adverse events.

Data on socioeconomic status and QoL are limited.
Data on socioeconomic status and quality of life (QoL) vary between the registries. The only countries collecting socioeconomic data are Sweden and Finland, where, e.g., data on education and employment are included. QoL is included in some of the registries. The QoL instrument most often used is EQ-5D; however, examples of instruments are included that might be more relevant for rare bleeding disorders.

Source: (1) BTC – Guidelines on the management of asthma (Link)

Executive summary (2/2)

Not all registries publish annual reports. However, aggregated data are available from most registries.

Seven of the registries evaluated publish annual reports. However, their structures are different, which limits comparisons between countries. The differences in annual reports reflect the different backgrounds of the registries and the differences in variables collected.

The most significant hurdle for collaboration is the consent provided by the patients. For example, the consent provided in Greece prohibits the registry from participating in collaborations. Other registries have well-established collaborations with payers and governmental agencies, e.g., in Sweden, where the registry is one of the official quality registries.

The ability to share data varies between registries. Some registries cannot share any data due to legislation, whereas other registries can share patient-level data, including patient identifiers, for research purposes. We identified information on sharing of data from ten registries, seven of which share anonymised data. However, sharing data with the pharmaceutical industry is limited for most registries.

There are some opportunities for the future.

PRO data can be included in registries if patients can submit the data themselves. Denmark, Ireland, and the UK are testing to enable patients to provide PRO data directly to a registry. If this work is synchronised between countries, economies of scale are possible.

Aligned annual reports can serve as a foundation for combined reports and as an inspiration for countries without registries, so aligning annual reports is a future possibility. We identified that seven registries currently publish an annual report. For countries that do not have a registry yet, the annual reports can be an inspiration for what to include in a registry.

An agreement on a common CRF to be used would enable synchronised analyses across multiple countries.

The largest opportunity lies in planning synchronised analyses across the registries. We identified hurdles in sharing data, so any analysis involving multiple registries needs to be performed at each registry and summarised at a later stage. Setting up a governance structure for, e.g., how research questions are selected and who can initiate studies will be vital.

If the registries are to be used in evaluating treatments in the real world, a well-defined governance structure is needed to determine who can be a collaboration partner.

Source: (1) BTC – Guidelines on the management of asthma (Link)

Abbreviations

CRF	Case Report Form
EHC	European Haemophilia Consortium
HA	Haemophilia A
HB	Haemophilia B
vWD	von Willebrand Disease
PRO	Patient Reported Outcomes
QoL	Quality of Life

CHAPTER 1
Overview of the registry landscape across Europe

CHAPTER 2
Deep dive into country-specific registries

REFERENCES

CHAPTER 1

OVERVIEW OF THE REGISTRY LANDSCAPE ACROSS EUROPE

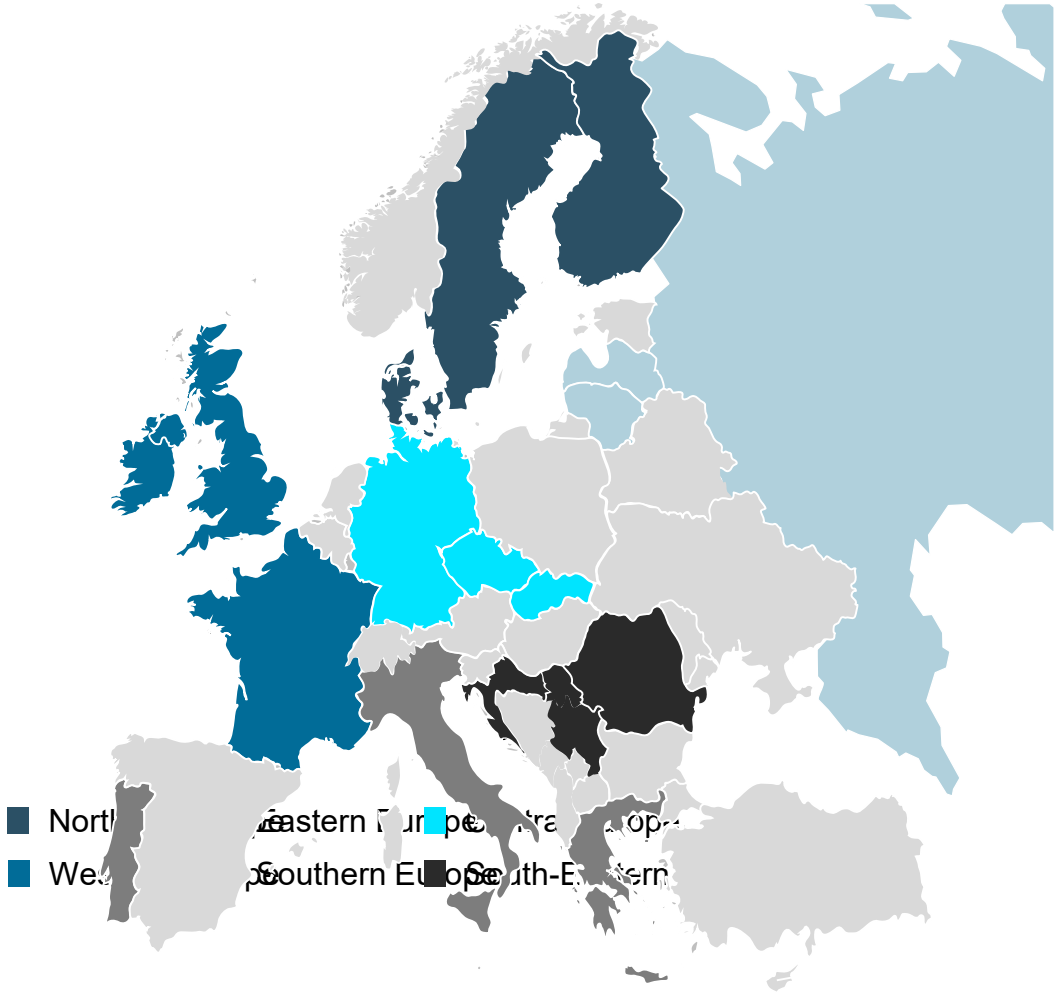
Countries included in the registry mapping

Mapping registries for rare bleeding disorders in Europe

We mapped out registries in 18 countries in six geographical regions:

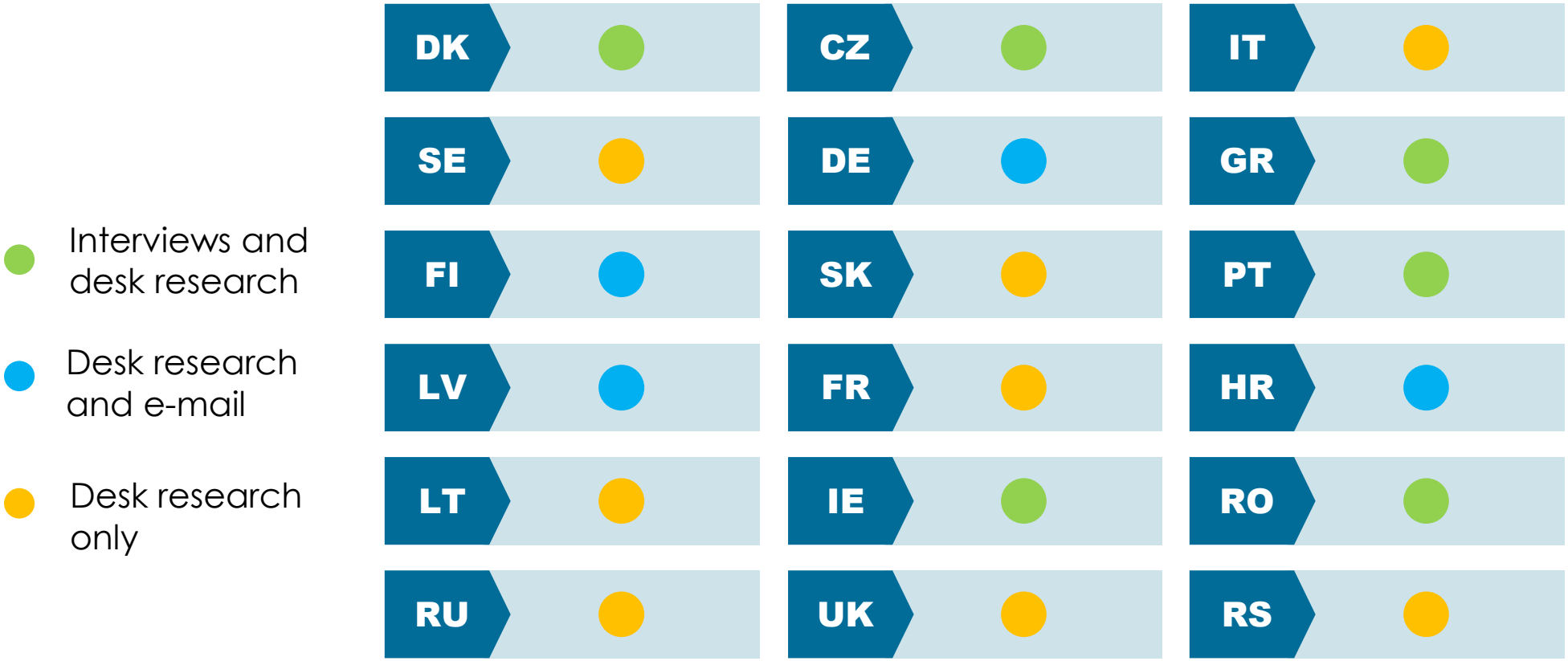
- Northern Europe: Denmark, Finland, Sweden
- Eastern Europe: Latvia, Lithuania, Russia
- Central Europe: the Czech Republic, Germany, Slovakia
- Western Europe: France, Ireland, the UK
- Southern Europe: Italy, Greece, Portugal
- Southeastern Europe: Croatia, Romania, Serbia

The analysis is based on a combination of desk research, interviews, and written responses from representatives of the national registries.



Type of research conducted (desk research vs. interview)

We conducted desk research in all 18 countries. In six of these countries, we also conducted interviews with representatives of the respective registry. In four countries, we also received information by e-mail.



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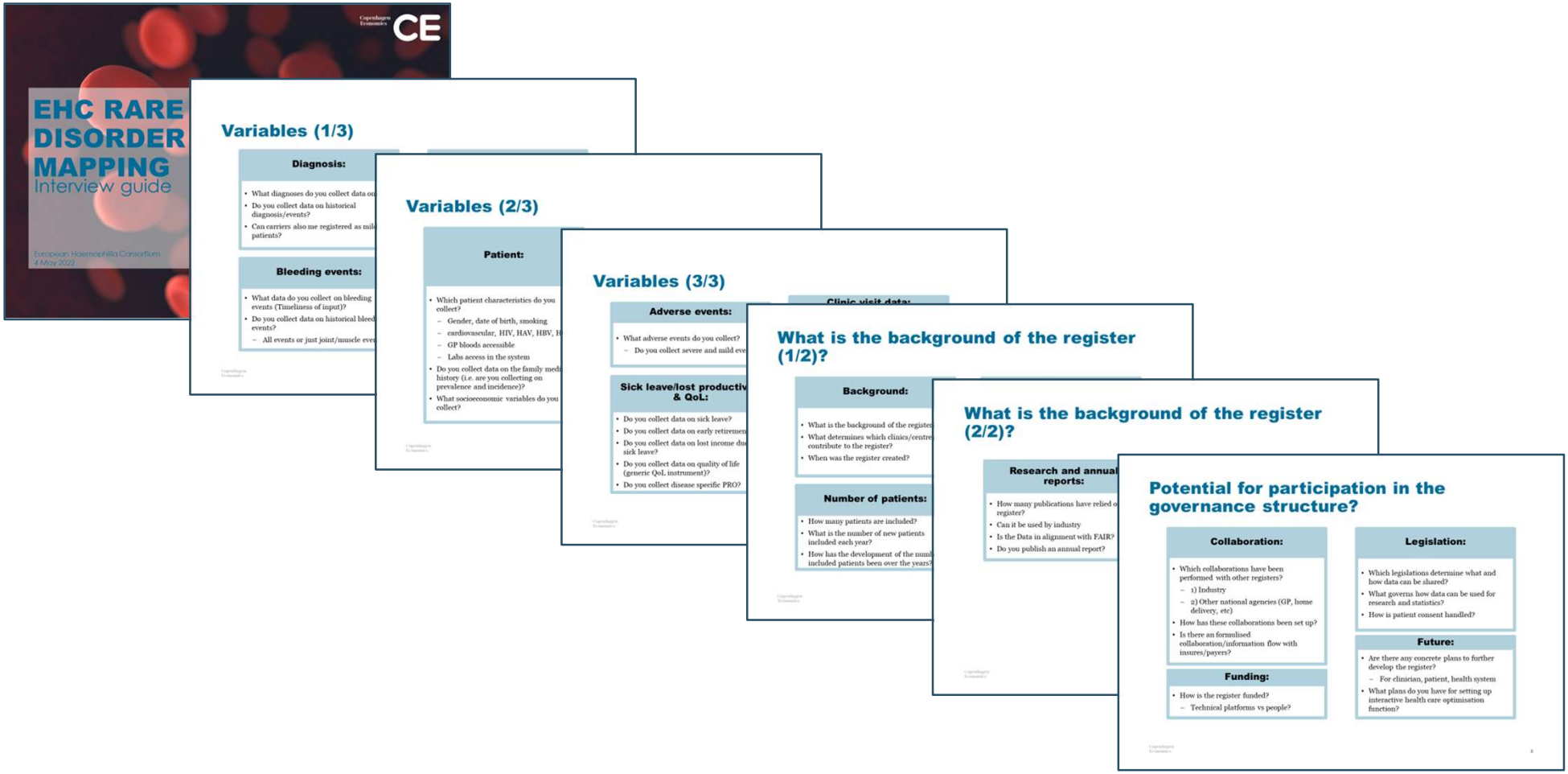
The interviews centred around questions on background, variables, and potential collaborations.



The objective of the interviews was to identify similarities and differences among the disease registries.

Principles for an ideal registry

What is the background of the registry?	Background information such as how the registry was developed or which treatment centres participate
How are the data collected? Is it done systematically?	Longitudinal data collected automatically
Does the registry publish an annual report?	The registry publishes an annual report
What diagnoses do you collect data on?	Collection of current diagnoses is sufficient if data are collected longitudinally
Do you collect data on all bleeding events?	Collection of all bleeding events, not only joint and muscle bleeding
What treatments do you collect data on?	Collection of the type of treatment and dosage

Principles for an ideal registry

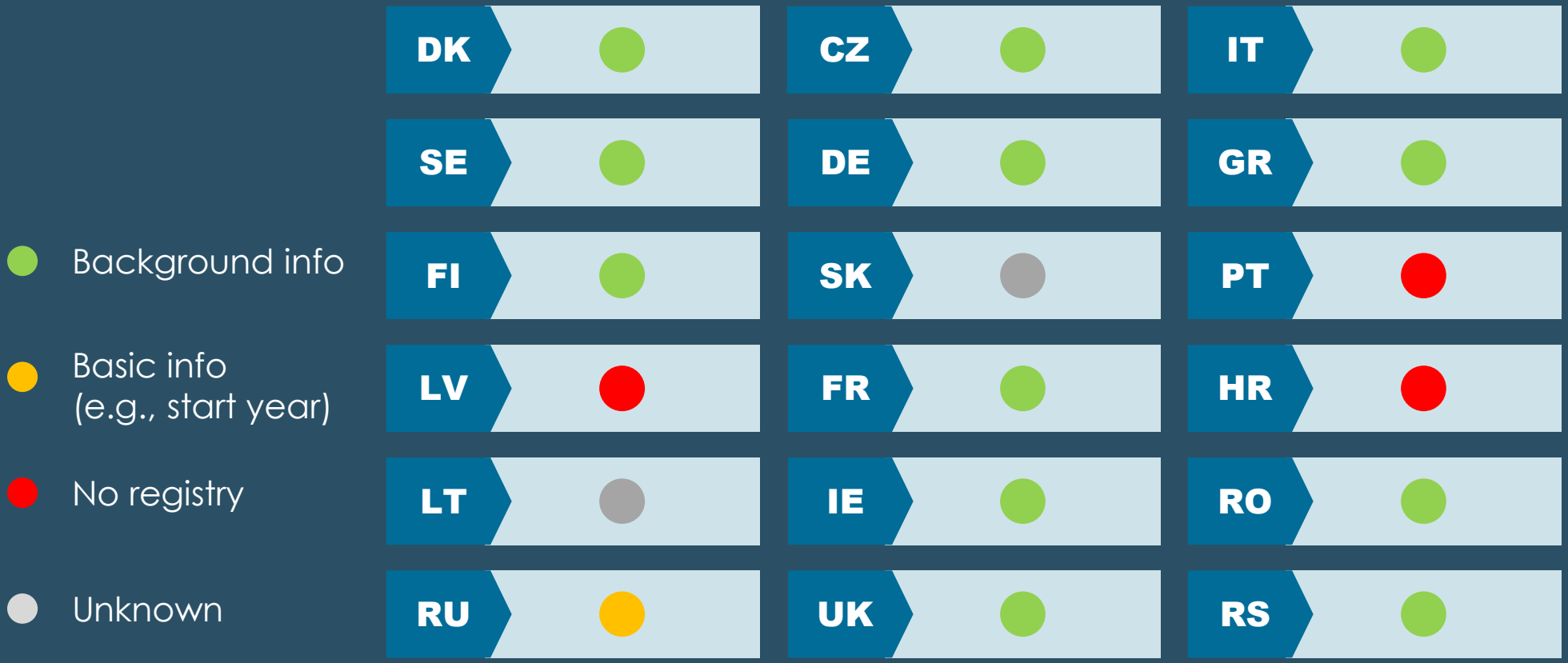
What patient variables do you collect?	Patient data including demographics, family medical history, and socioeconomic status
Do you collect data on adverse events?	All adverse events collected, including coinfections, inhibitors, and other side effects
Do you collect data on sick leave, PRO, and QoL?	Collection of sick leave and related income losses, PRO, and QoL data
How can data be shared for academic research?	Sharing of anonymised patient-level data for academic research
Are there concrete plans to develop the registry further?	Plans to automate data capturing and link data to different sources are in place

Collaborations and data sharing with the pharma industry are categories up for discussion.

Do you have structured collaborations?	Collaborations with other registries, payers, or industry are in place
	No collaborations are in place
Is it possible for the pharma industry to get data for analysis?	Sharing of anonymised patient-level data with industry
	Sharing of aggregated data with industry
	No sharing of data with industry

What is the background of your registry?

We found national registries in 13 out of 18 countries. In 12 countries, we identified background information such as how the registry was developed or which treatment centres participate. In Russia, we only identified the starting year of the registry.



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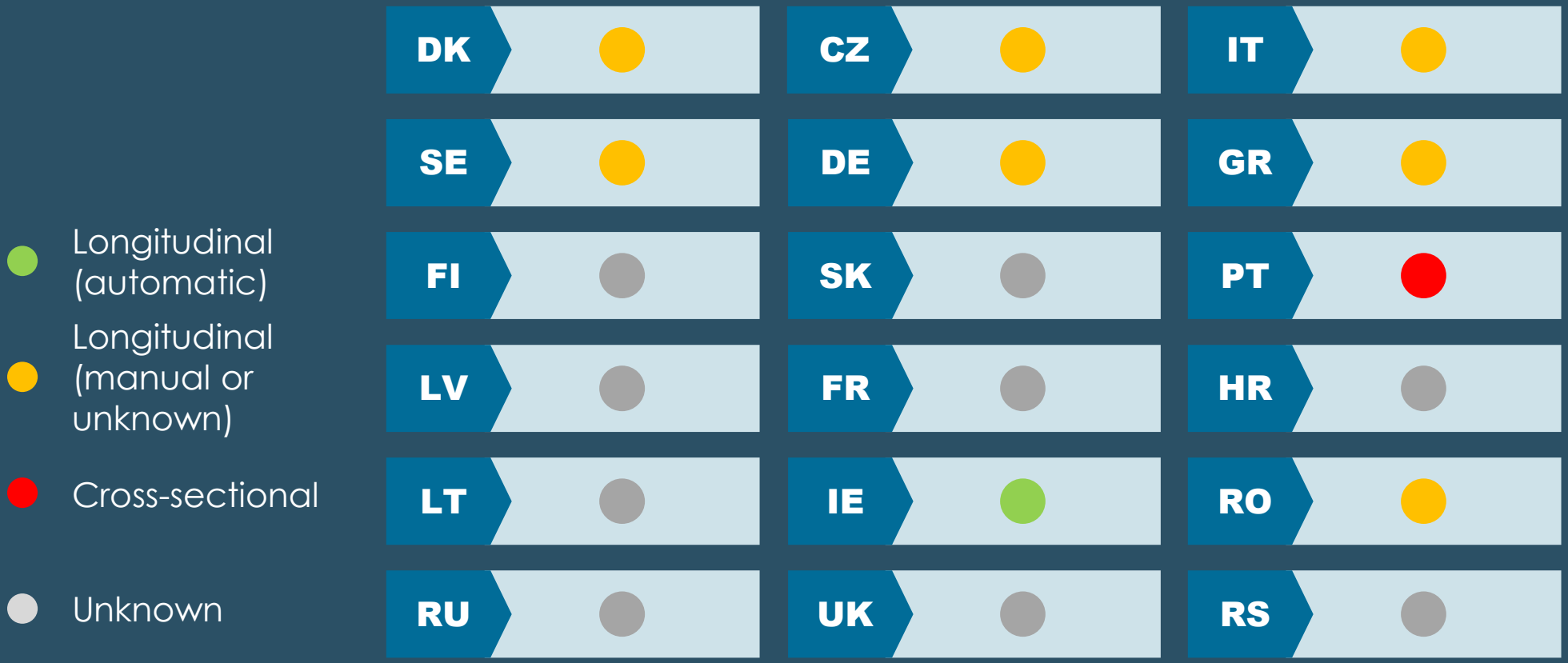
How are the data collected? It is done systematically?

In nine countries, we determined the type of data collection, i.e., whether data are collected cross-sectionally or longitudinally and whether data are automatically or manually transferred to the registry. In eight countries, data are collected longitudinally. Ireland is the only country in which data are automatically transferred to the registry. Portugal only collects cross-sectional data.



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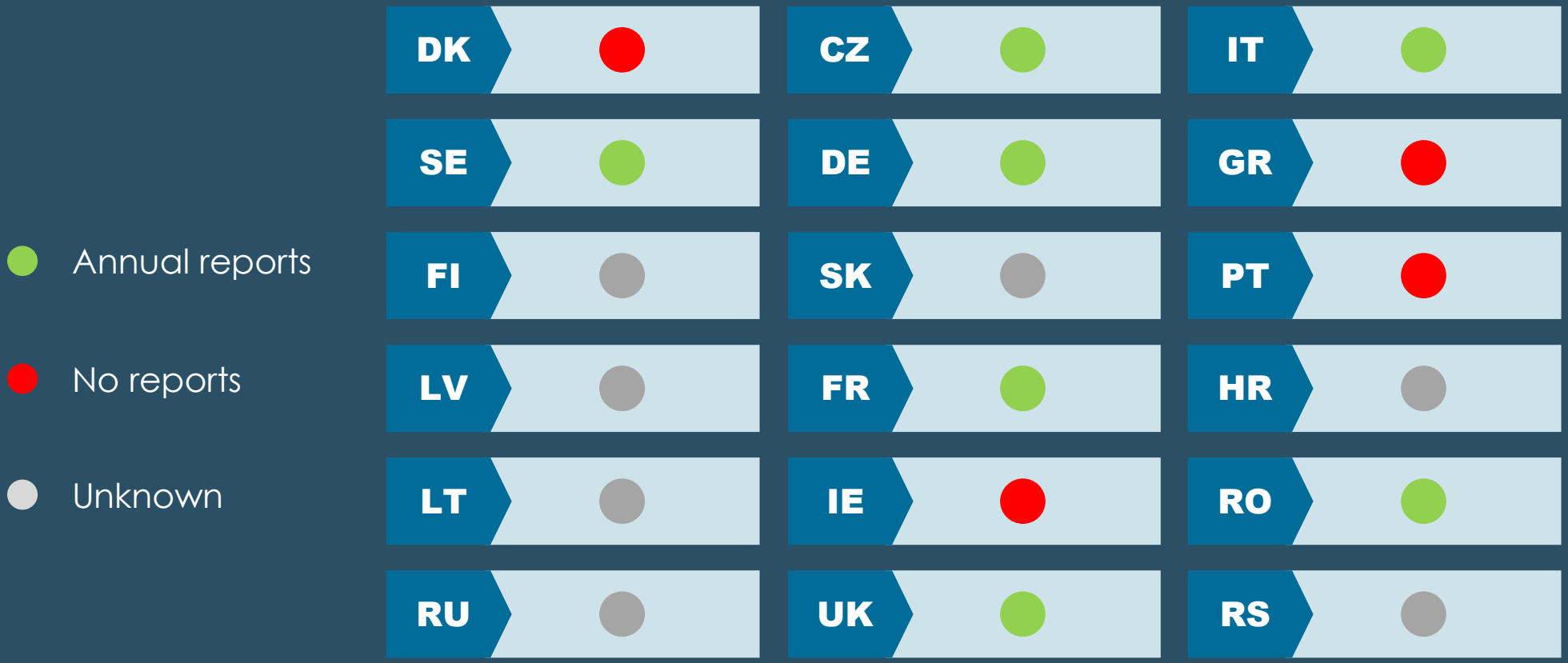
Does the registry publish an annual report?

We found information on registry publications for 11 countries. Seven countries publish annual reports, whereas four countries do not.



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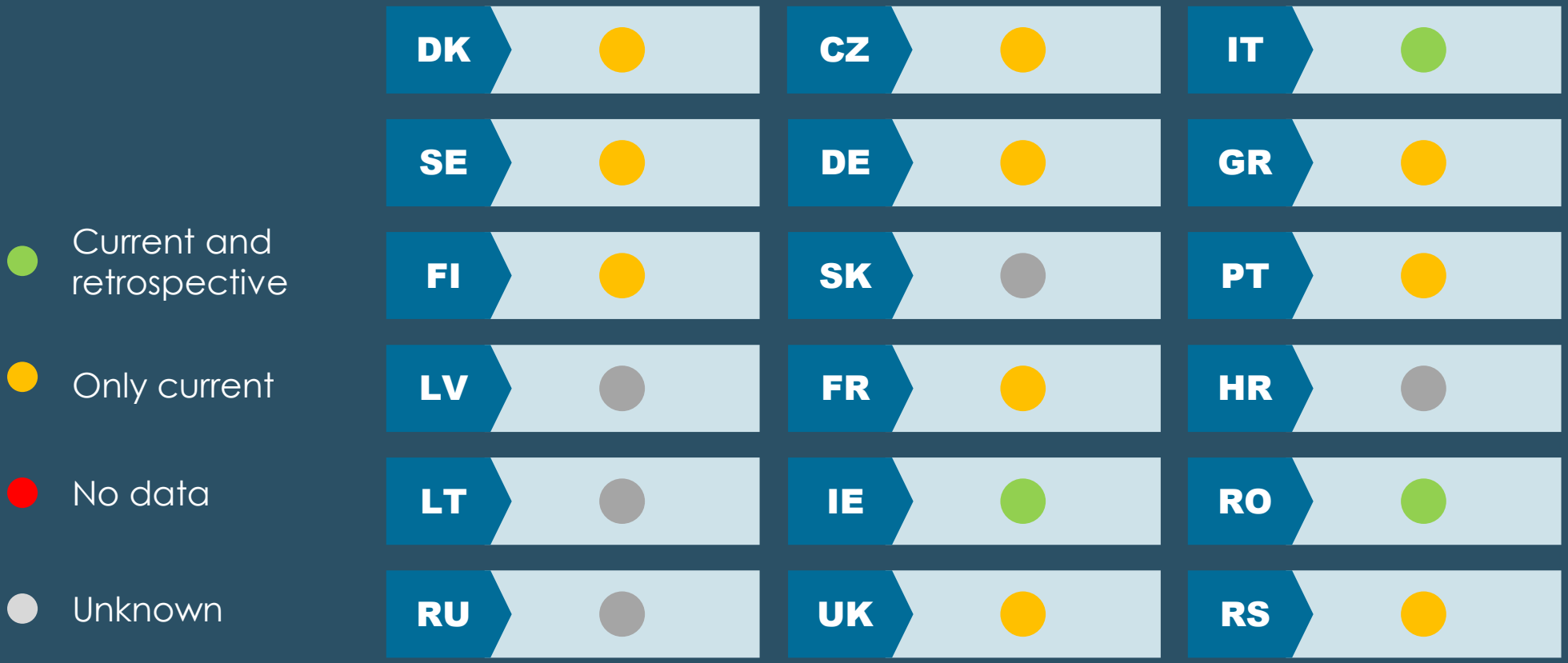
What diagnoses do you collect data on?

We identified information on covered diagnoses in 13 registries. Ten out of 13 countries only collect data on current diagnoses, whereas three countries also collect diagnoses retrospectively.



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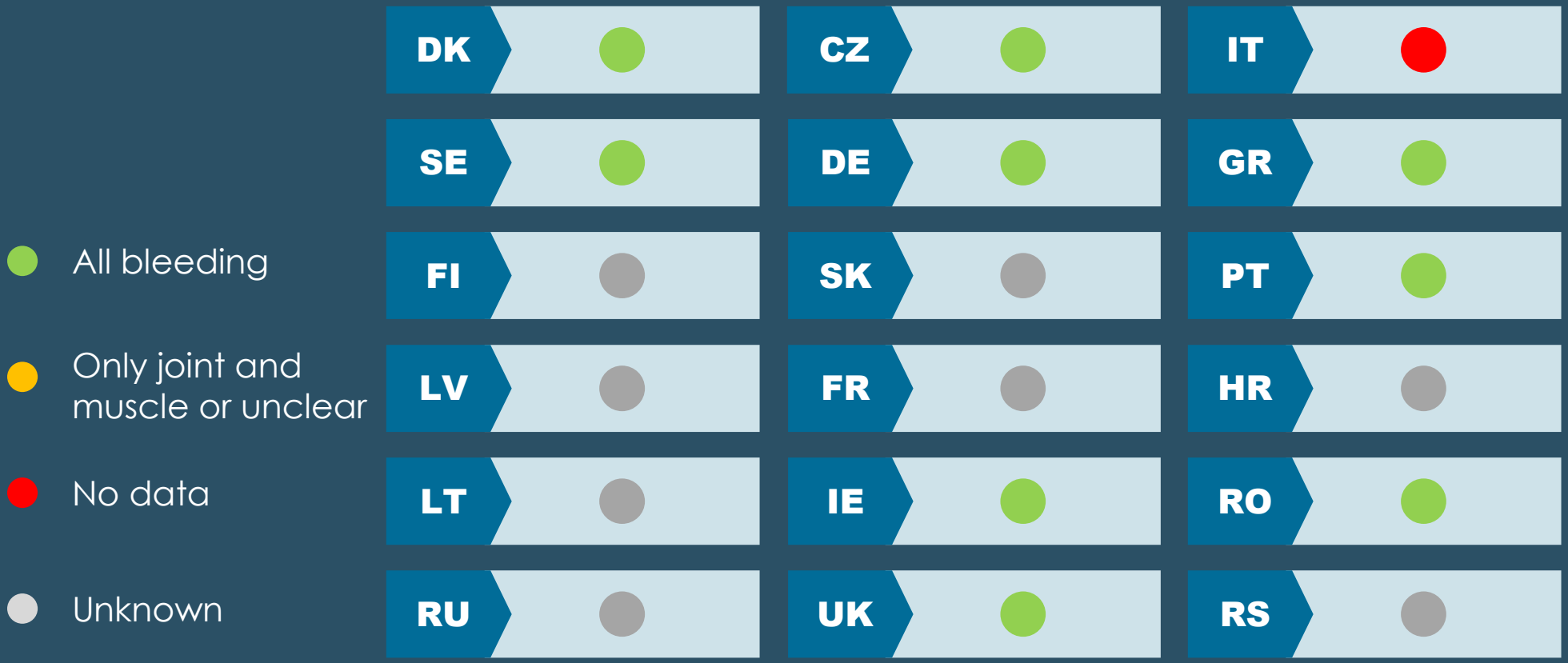
Do you collect data on all bleeding events?

We found information on bleeding events in ten registries. Nine out of ten registries collect data on bleeding events. None of them exclusively collects data on joint and muscle bleeding. Italy does not collect data on bleeding events.



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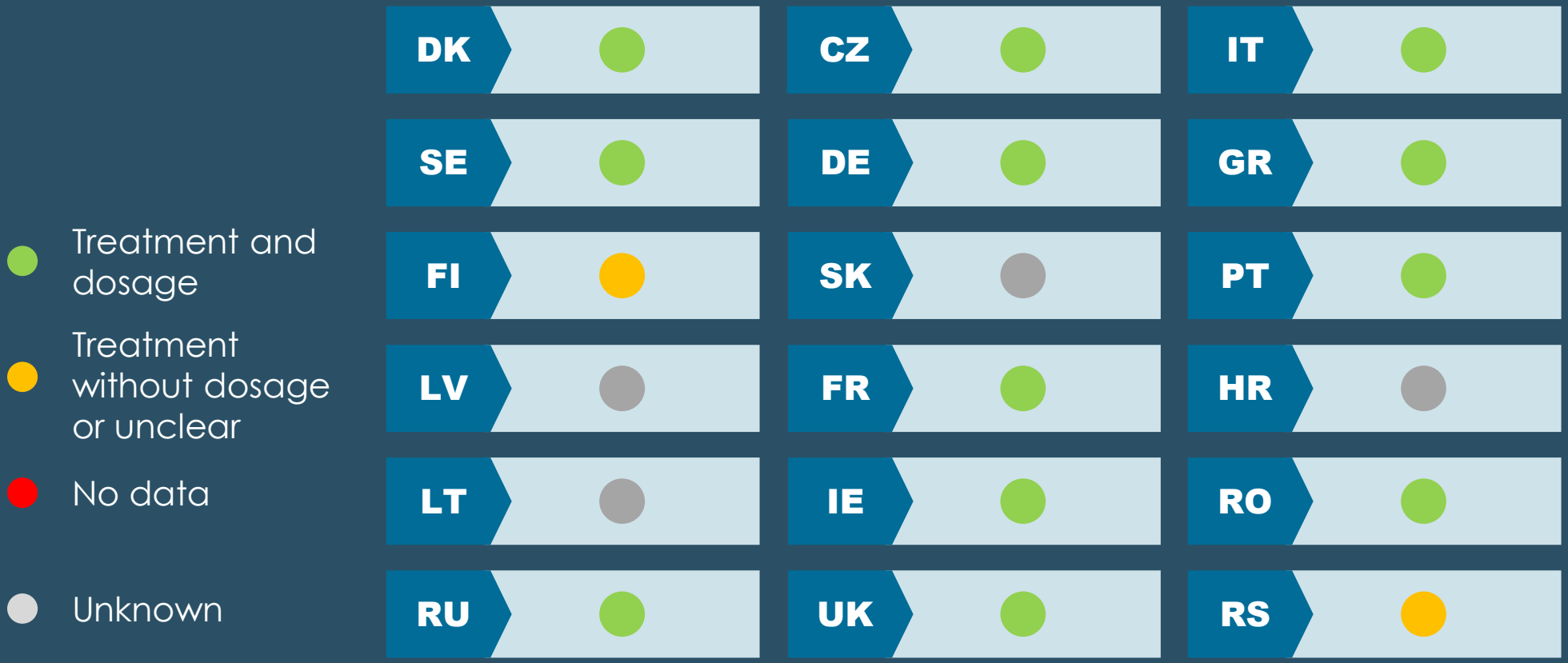
What treatments do you collect data on?

We identified information on covered treatments in 14 registries, 12 of which collect data on treatment type and dosage. Two registries (Finland and Serbia) collect treatment information, but it is unclear whether they collect data on dosage.



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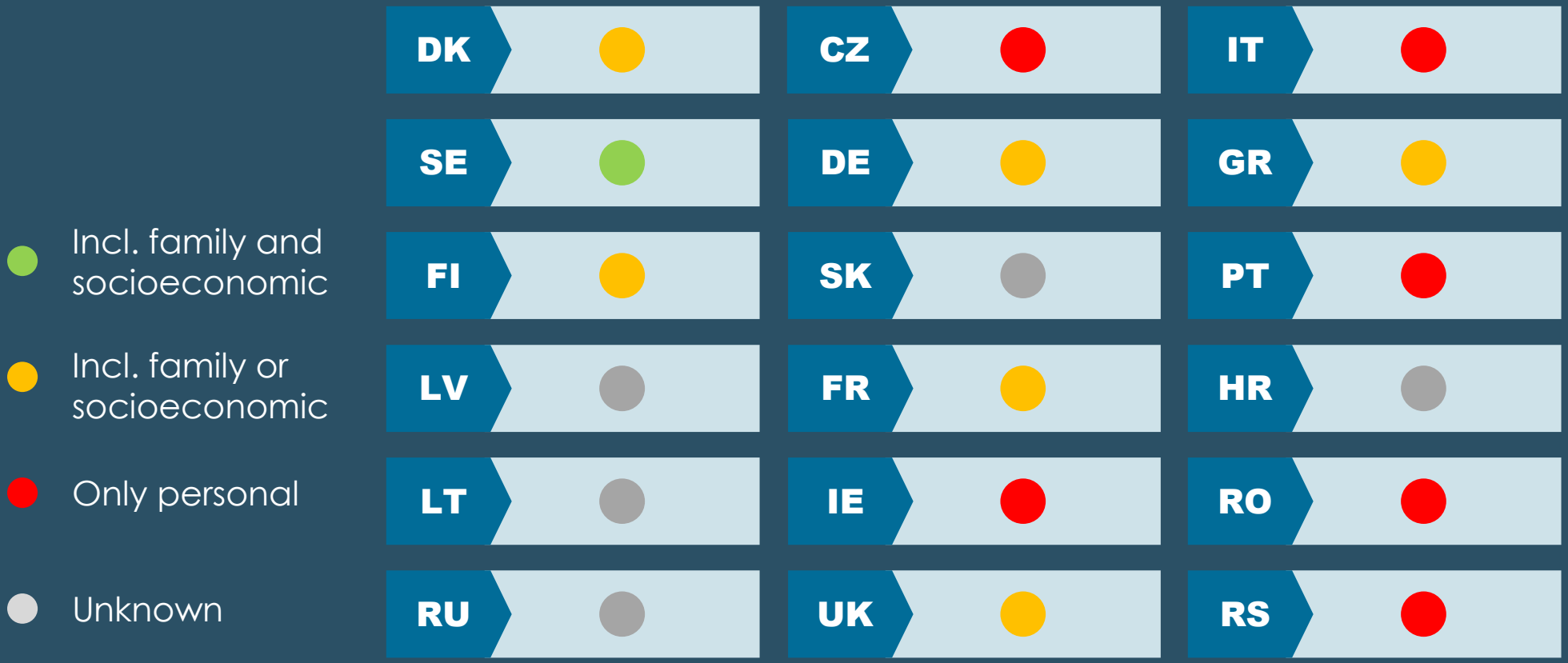
What patient variables do you collect?

In 13 countries, we identified the patient variables collected in the registry. Only the Swedish registry collects patient data (e.g., age, sex, lab results) and information on both family medical background and socioeconomic variables (e.g., education, employment). Six registries collect patient data and either family medical background or socioeconomic variables. Another six countries only collect patient data but no information on family medical history or socioeconomic variables.



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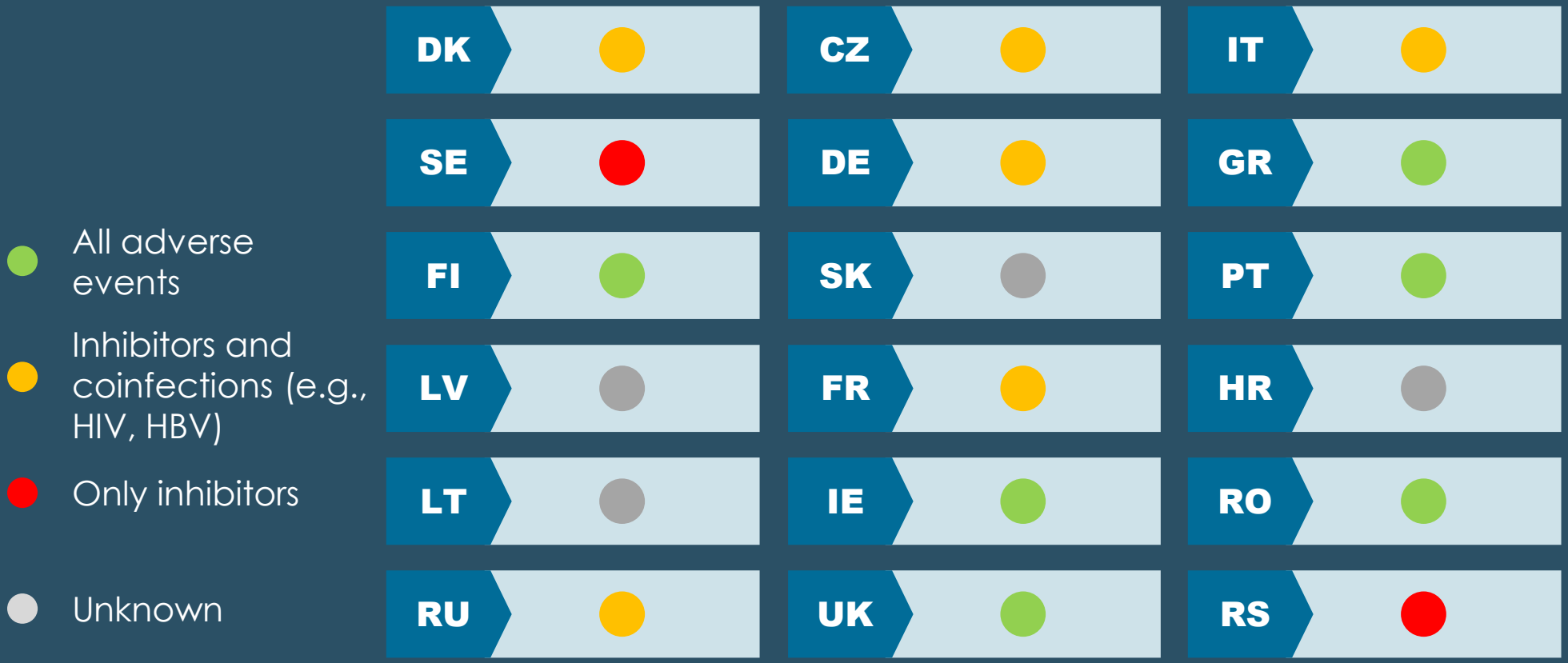
Do you collect data on adverse events?

We identified 14 registries that collect data on adverse events. Six registries only collect information on disease-specific adverse events, such as inhibitor development or coinfections (e.g., HIV, hepatitis). Six countries also collect all adverse events, such as allergic reactions. Two countries only collect information on inhibitor development.



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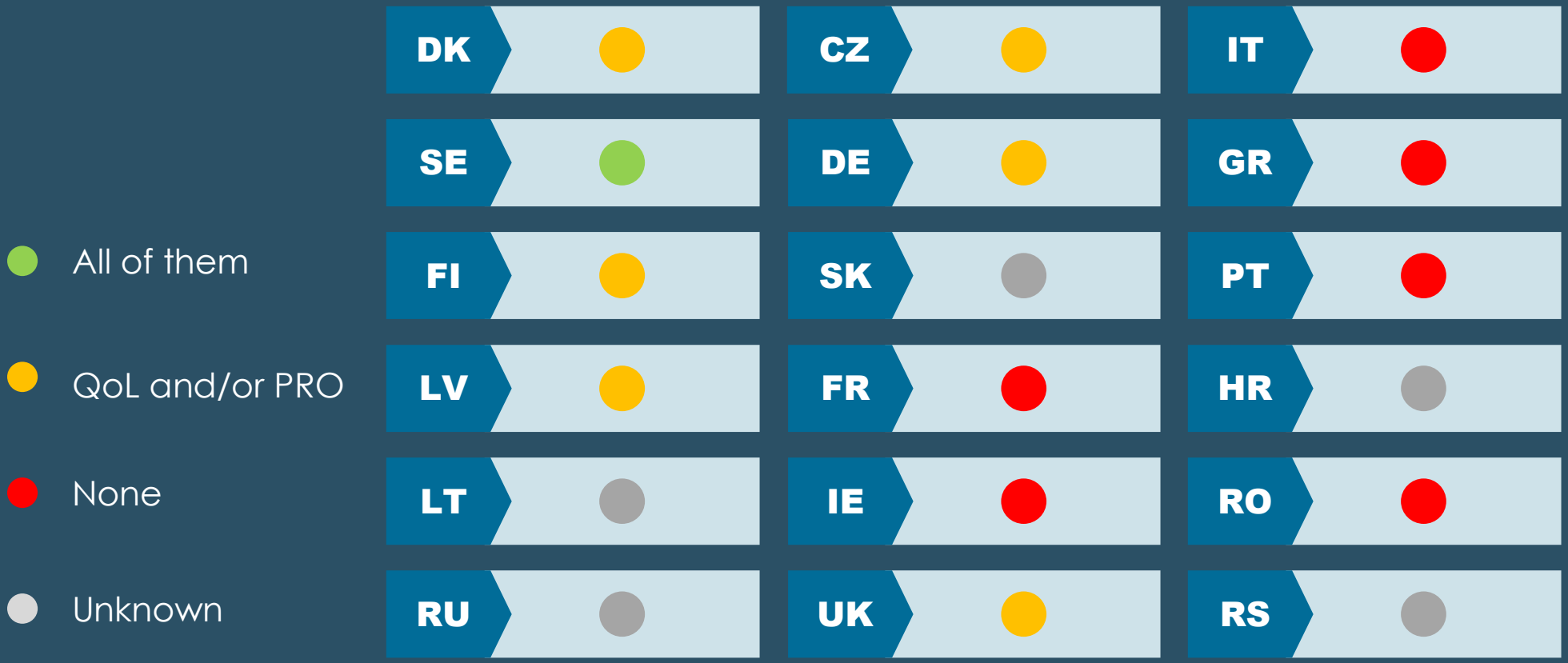
Do you collect data on sick leave, PRO, and QoL?

We identified 13 registries that report on whether they collect data on the impact of the disease on patients' lives. While Sweden collects data on sick leave, PRO, and QoL, six registries only collect some of these variables. Six countries reported that they do not collect any such information. Overall, five QoL instruments were used by the registries reviewed: EQ-5D, EQ-5D-5L, Haemo-QoL, EDUARDO REMOR, and PILAR ARRANZ.



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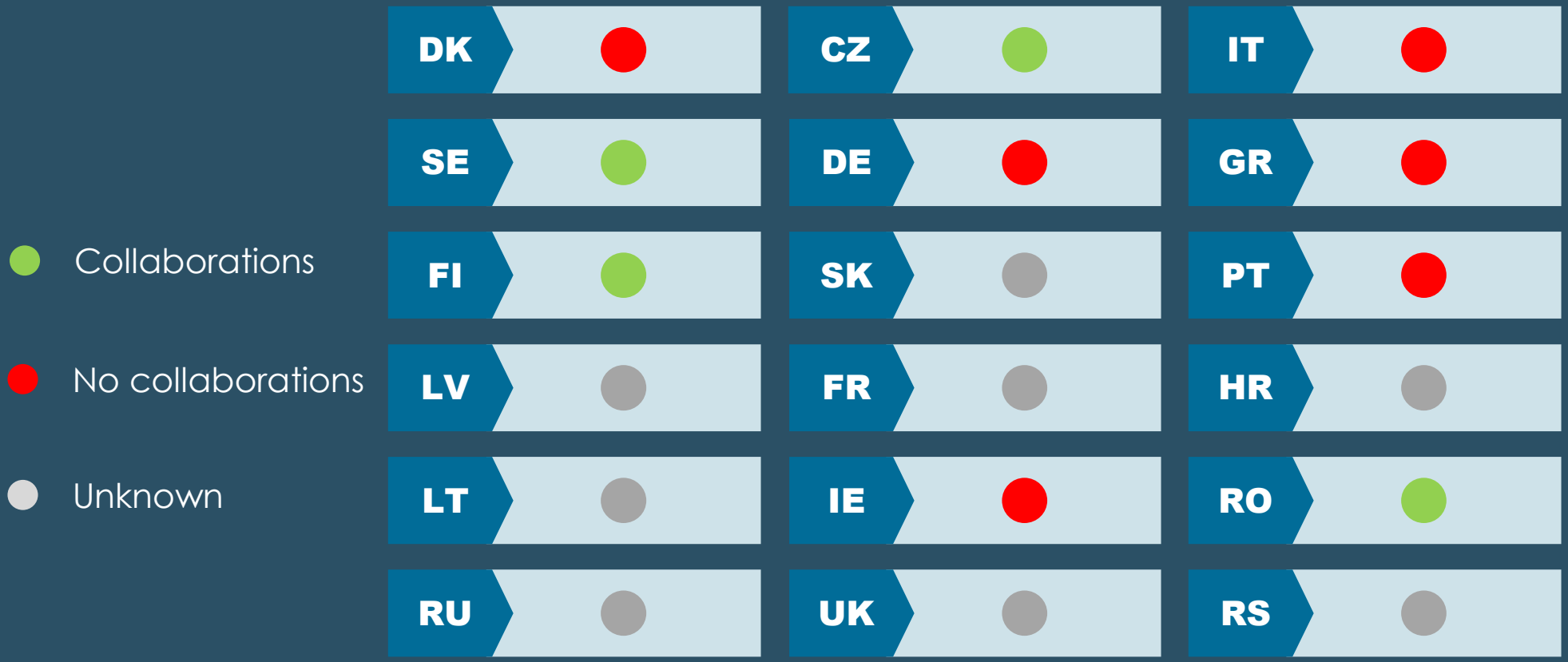
Do you have structured collaborations?

We identified information on collaborations in ten registries. Four registries have collaborations in place, whereas the other six do not. Most collaborations are with associations or payers in the same country, but the Czech registry is also linked to the WAPPS-Hemo database in Toronto and Hamilton.



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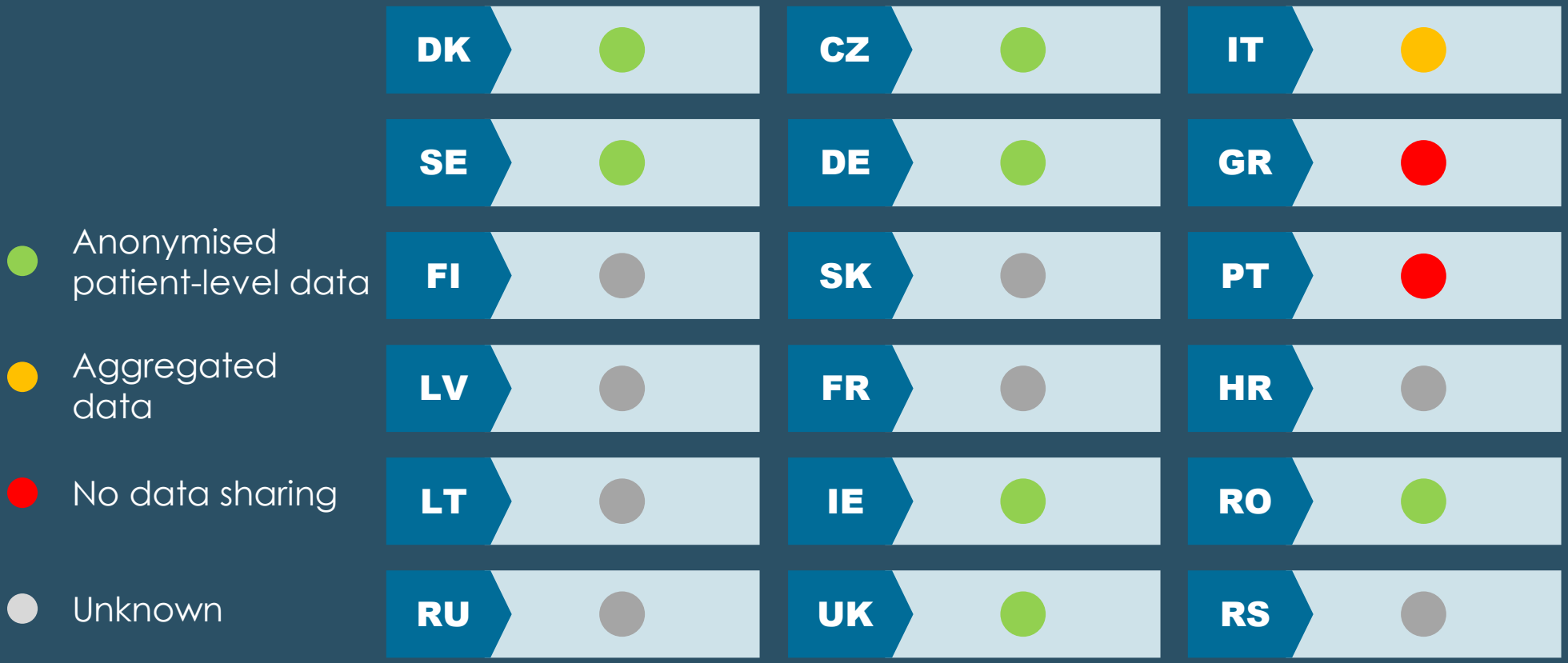
How can data be shared?

We identified data-sharing policies in ten countries. Seven allow sharing of anonymised patient-level data for scientific research purposes. One country only shares aggregated data and two countries do not share data for scientific research at all.



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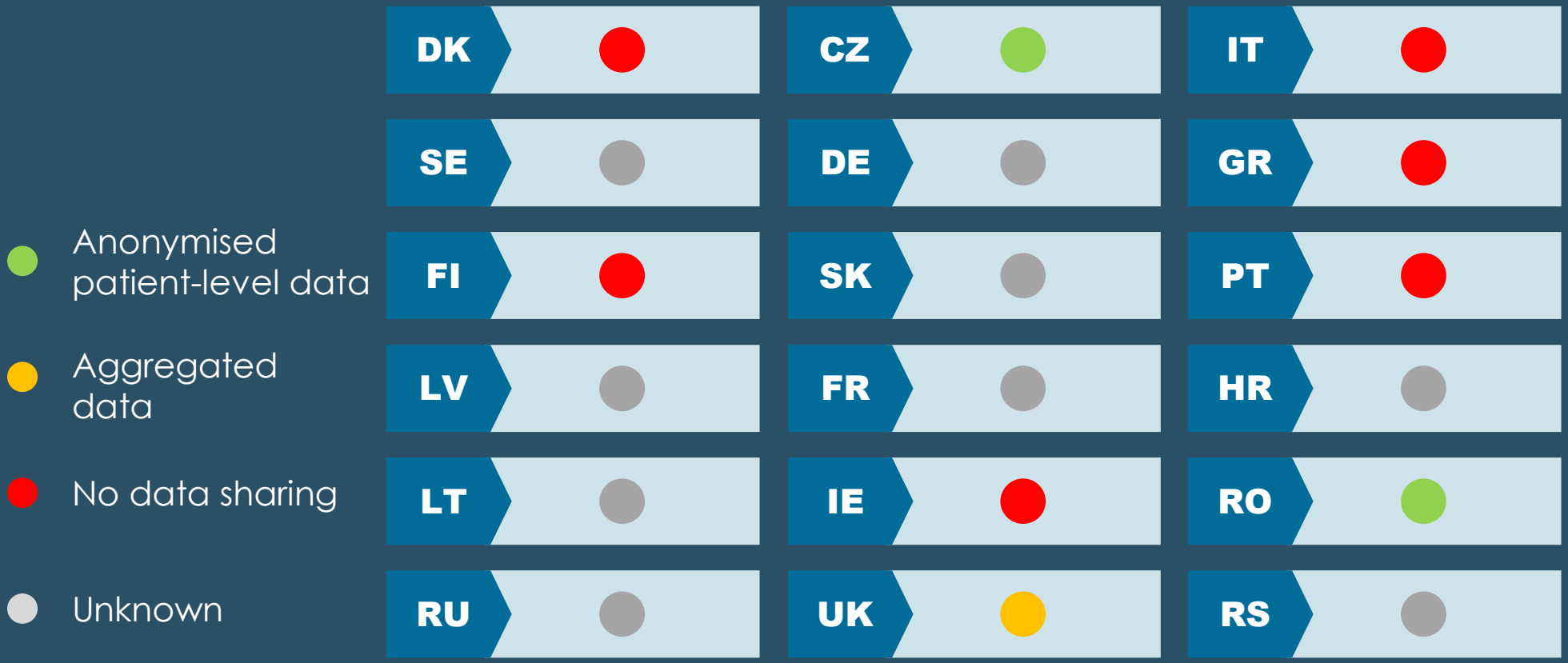
Is it possible for the pharma industry to get data for analysis?

We identified data-sharing policies with the pharma industry in nine countries. The pharma industry can get access to the Czech and Romanian registries. The UK shares aggregated data with the pharma industry. The remaining six countries do not share any data with the pharma industry.



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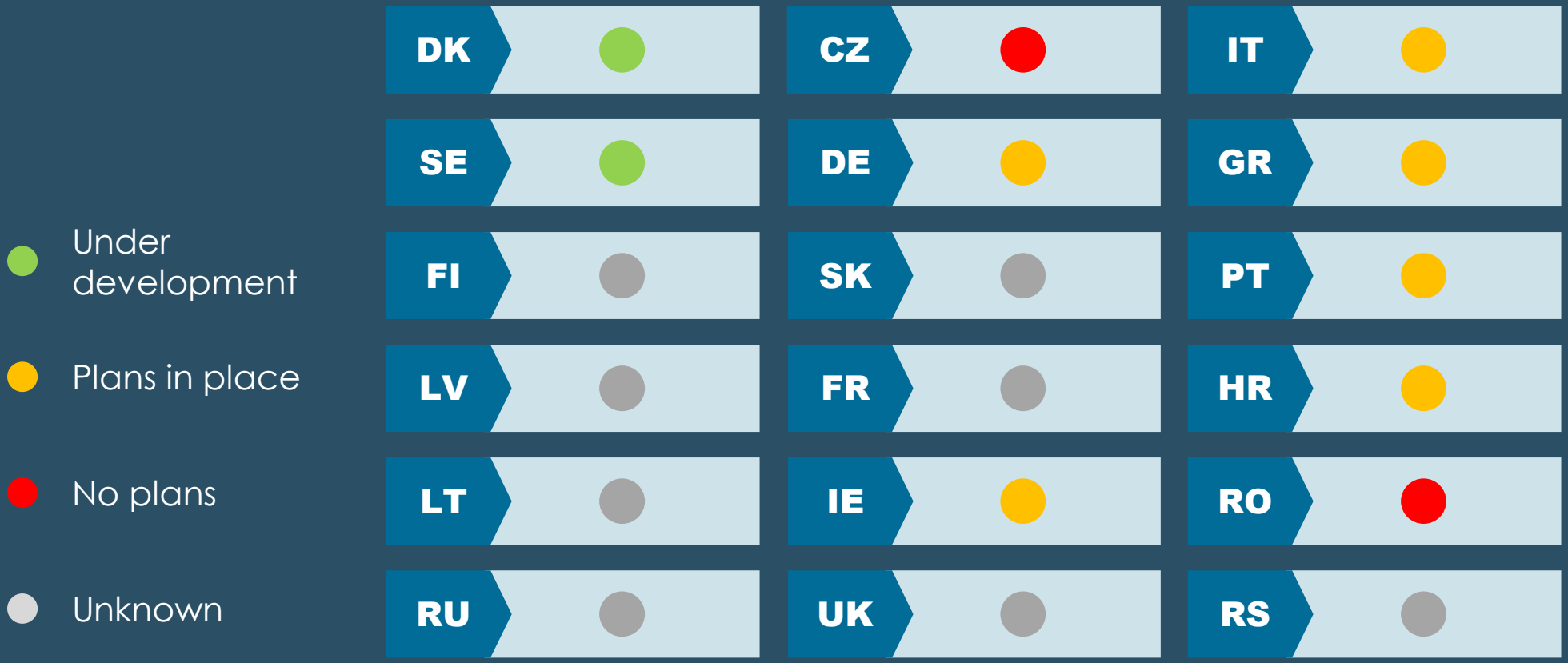
Are there concrete plans to develop the registry further?

We identified plans for further development of the registry (or the absence thereof) for ten countries. Two countries are developing or have already developed these plans, whereas six countries have only articulated plans for further development. The Czech and Romanian registries have no plans to make structural changes to their registries.



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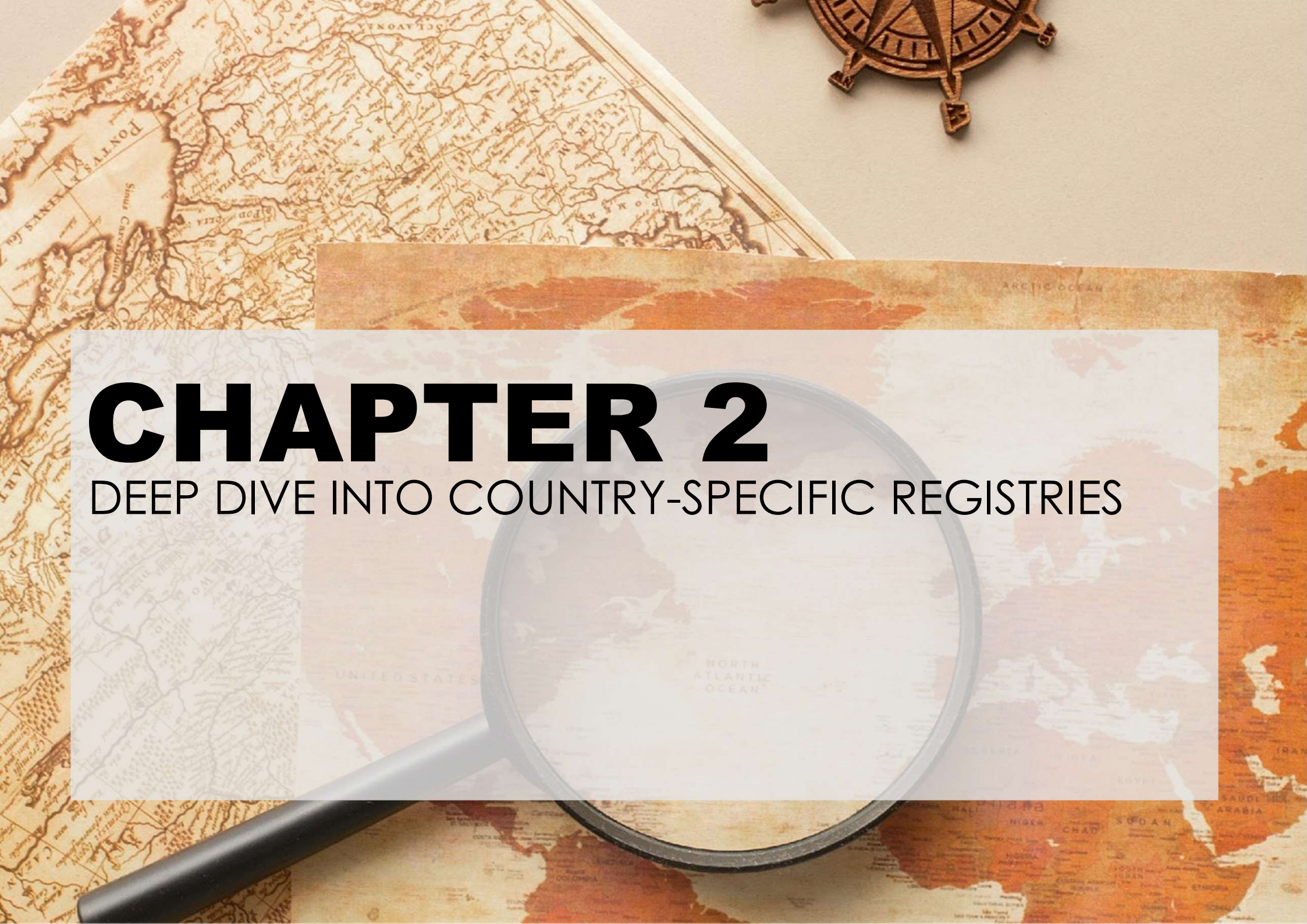

CHAPTER 2

DEEP DIVE INTO COUNTRY-SPECIFIC REGISTRIES

A national Danish registry for rare bleeding disorders is currently under development.

Background

A national registry is under development.

- Currently, Aarhus University Hospital and Rigshospitalet (Copenhagen) have separate registries.
- Data collection goes back to the 1970s. However, structured data have only been collected for approximately ten years.
- A pilot project has been conducted to develop a new rare bleeding disorder database combining hospital data and PRO data through app usage.

Data are representative on a national scale.

- Around 600 patients in Aarhus University Hospital have various rare bleeding disorders.

Electronic, separate data collection

- Patient-level data are collected electronically by healthcare workers at the clinic (physicians, nurses, physiotherapists).
- Data are longitudinal and updated in real-time.
- The registry is separated from electronic medical records (EMR).
- No annual reports or other publications are based on the registry.

Variables collected

Basic patient information

- Patient data include demographics such as age and family history of rare bleeding disorders and quality of life scores (EQ-5D).
- No collection of sick leave and associated income loss, early retirement, or socioeconomic variables.

Diagnosis, bleeding events, and treatments are reported at the patient level.

- The registry reports the patient's diagnosis, its severity, the presence of other bleeding disorders, joint scores, and bleeding events. Historical diagnoses and bleeding episodes are only recorded if clinically relevant.
- Treatment data include drugs and their dosages. Patients on prophylaxis can use an app to report their treatment and bleeding events. These data are not currently stored in the registry but may be added in the future.

Major adverse events such as inhibitor development or infection with HIV and HCV are reported.

- Other side effects are only stored in the electronic patient records but do not feed into the registry.

Governance structure

Data processing and sharing are strictly regulated.

- The Danish Data Protection Act and the Health Act determine how and what kind of data can be shared.
- Informed, signed patient consent is needed to permit third-party access to medical records from the registry.
- Data may be used for scientific research, but not by industry.

The hospitals provide funding to enable data collection.

- Both the technical platform and the staff are funded by the hospital.

Legal challenges hinder continued collaboration with other registries.

- Between 2008 and 2019, a collaboration with EUHASS existed.
- Data protection requirements imposed legal hurdles, which is why the collaboration ended.

The app is the future.

- The app development will continue and is supposed to become a vital part of the registry, adding PRO.

Source: Interview with a representative from Aarhus University Hospital; Danmarks Bløderbehandling https://www.bloderforeningen.dk/om-foreningen/projekter/telemedicin/ (accessed 27-05-2022); Region Midtjylland https://www.rm.dk/sundhed/faginfo/center-for-telemedicin/projekter-og-indsatser/Beslutningsstotte-i-bloderbehandling/udvikling/database-til-pro/ (accessed 27-05-2022).

The Swedish Haemophilia Registry is well developed.

Local name: **Svenska Hemofili Registret (SHR)**

Background

The national registry combines three Swedish treatment centres.

- The national registry was established in 2012.
- It includes data from patients treated in Sahlgrenska University Hospital Gothenburg, Skåne University Hospital Malmö, and Karolinska University Stockholm.

The registry covers 100% of the affected population.

- In April 2021, 1,929 patients with HA, HB and vWD were recorded.
- 817 new patients were recorded between 2020 and April 2021.

Data are collected electronically.

- Data are collected electronically by clinicians in the hospital.
- Data are updated annually.
- The data structure is longitudinal, following the same patients over time.
- Annual reports have been published since 2017.

Variables collected

Patient information is detailed.

- Patient data include date of birth, sex, weight, height, smoking/snus/alcohol consumption.
- Records include family history of bleeding disorders and socioeconomic variables (working/studying/jobseeker, working conditions, highest level of education, pension), and quality of life (EQ-5D).
- No collection of early retirement or lost income due to sick leave.

Diagnosis, bleeding events, and treatments are reported at the patient level.

- The registry reports the patient's diagnosis (HA, HB, vWD) and bleeding events including date of bleeding, bleeding units, location of bleeding, whether bleeding occurred after pain/swelling/movement/impairment, etc.
- Treatment covers medication including dosage and surgery, home treatment, and concomitant immunomodulatory therapy.
- In the long run, inclusion in the registry of patients with unusual coagulation factor deficiencies is planned.

Only major adverse events are recorded.

- Adverse events include inhibitor development.

Governance structure

Swedish data protection laws determine data sharing.

- The Personal Data Act, the Swedish Patient Data Act, and the Swedish Patient Security Act govern data collection and sharing with third parties.

Local and global collaborations

- Since its initiation, the Swedish Haemophilia Registry has been connected to the Quality Registry Center Stockholm, which supports national quality registries.
- The Swedish Haemophilia Registry forms the basis for a new global platform, the World Bleeding Disorders Registry (WBDR), which has been developed by the same IT provider, Health Solutions. Representatives from the SHR's steering group have contributed to the development of the global registry.

Interactive health care optimisation is in place.

- Patients' treatments and registered symptoms can be shown graphically over time.

Source: Public documentation of the Svenska Hemofili Registret https://svenskahemofiliregistret.se (accessed 08-06-2022); Holmström et al. (2021) - Real-world prophylactic usage of recombinant factor VIII Fc in Sweden: A report from the Swedish national registry for bleeding disorders; Information on the legal governance structure is obtained from https://ec.europa.eu/health/system/files/2016-11/laws_sweden_en_0.pdf and https://www.timelex.eu/sites/default/files/2019-01/29.%20Swedish%20legal%20framework.pdf (accessed 27-05-2022).

The Finnish Haematology Registry is an independent, research-oriented registry.

Local name: **Suomen hematologinen rekisteri**

Background

The national registry is owned by the Finnish Association of Haematology.

- Records patient data from all treatment centres for blood diseases, i.e., 5 university hospitals, 16 central hospitals and all health care districts in Finland.
- 22,000 patients with various haematological diagnoses were included in the registry in 2018.
- The registry was founded in 2007*.
- The registry has been complemented by a biobank (FHRB) since 2014-2015. Biobank collects biological samples (e.g., data from the registry, blood pressure, etc.) for future research and development of healthcare products.

Data collection takes place in the treatment centres.

- Data are collected from patient records in the treating units by research nurses or doctors and stored electronically.
- Additional data can be added from the Population Registry, the Finnish Cancer Registry, Statistics Finland's Deaths and Discharge/Treatment Notification Registry of Hospitals, archives, and local registries.

Variables collected

Collection of patient and socioeconomic characteristics and quality of life

- Patient data include sex, age, marital status, smoking status, and lab results.
- Socioeconomic data cover educational background and employment status.
- Patient-reported outcomes including quality of life(EQ-5D-5L) measures are collected in the registry as part of routine follow-ups, but not yet systematically.

Reporting of key diagnostic and therapeutic variables

- Diagnoses include HA, HB, vWD, and malignant haematological diseases.
- Both treatment and treatment responses are collected in the registry.

Wide coverage of adverse events

- Main side effects of the treatment (both typical and less common) and their management are recorded as adverse events.

Governance structure

Data processing and sharing are regulated by European law.

- The EU GDPR governs data processing and sharing.
- Participation in the registry is based on the written consent of the patient for the collection and registration of data.

Funding is provided by the Finnish Haematology Association.

- Funding covers all costs related to the maintenance and development of the registry.

Source: Public documentation from the Finnish Association of Haematology https://hematology.fi/fi/registry (accessed 29-04-2022): Suomen hematologinen rekisteri (SHR): väestöpohjainen seurantatutkimus koskien veritautien ja perinnöllisten verenvuototautien ilmaantuvuutta, esiintyvyyttä, diagnostiikkaa,hoitoja ja hoitotuloksia Suomessa; E-mail statements from representative of the registry from the HUCH Comprehensive Cancer Center; Biobank https://www.biopankki.fi/en/ (accessed 31-05-2022); Biobank https://www.biopankki.fi/en/ (accessed 08-06-2022).
*It has been launched for utilisation in 2010.

The Czech registry is well developed and includes granular diagnosis and treatment information.

Local name: Český národní hemofilický program (ČNHP)

Background

A well-developed national registry

- The registry lies within the Czech National Haemophilia Programme (CNHP) and aims at monitoring patients with inherited bleeding disorders.
- It was established in 2011 and builds upon its predecessor database, which collected disease counts from paediatric centres (ca. 20 years ago).
- The aim of the registry is to monitor treatment, facilitate scientific research, and contribute to the standardisation of registries across Europe.

Data are representative on a national scale.

- All treatment centres but one participate in the registry.
- The registry covered 1,658 patients in 2021.

Electronic data collection

- Patient-level data are collected electronically by data managers that work in each centre.
- Data are longitudinal and updated manually at least once per year.
- Data cannot be linked to other data sources.
- Annual reports have been published since 2011.
- At least 5 scientific publications have relied on the registry.

Variables collected

Thorough information on the patient's health and quality of life

- Patient data include demographics such as sex, age, height, weight, comorbidities, lab results, and quality of life measures (not systematically).
- No data on family medical history, socioeconomic variables, sick leave and associated income loss, early retirement, or disease-specific PRO.

Diagnosis, bleeding events, and treatments are reported at the patient level.

- The registry reports the patient's current diagnosis, its severity, the year of diagnosis, joint scores, and all bleeding events (including bleeding rate, bleeding score, location of bleeding, spontaneous or trauma, therapy, and associated hospitalisation).
- Treatment data include factor concentrates, prophylaxis, and other medication (including drug name, type, and dosage), surgery, home therapy, immune tolerance treatment (including concentrate used and dosage), and treatment of infections.

Major adverse events such as inhibitor development or infection with HIV and hepatitis are reported.

- Other side effects may be added but are not systematically collected.

Governance structure

Data processing and sharing are regulated by GDPR.

- Czech law and the EU GDPR regulate the collection and sharing of data.
- Anonymised data can be shared with third parties (both industry and scientific research) if patients provide signed informed consent.

The registry is funded by educational grants.

- Historically, the registry was funded by Masaryk University, Brno. Today, the registry receives external funding through educational grants (e.g., annual agreements with pharma companies).
- Additional funding is generated by fees associated with sharing of non-public data.

National and international collaborations

- The registry collaborates with health care payers around the country, national member organisations, and Hemojunior.
- The registry is linked to the WAPPS Hemo database in Hamilton and Toronto.
- The registry feeds WBDR of WFH with data and shares data with the State Institute for Drug Control (SUKL).

No structural changes are planned.

- The database is expected to change with the availability of new treatments.

Source: Czech National Haemophilia Programme (CNHP) https://www.cnhp.cz/index.php?pg=sit-center and https://www.registry.cz/index-en.php?pg=registries&prid=43#:~:text=The%20Czech%20National%20Haemophilia%20Programme,disease%20and%20other%20haemorrhagic%20disorders. (accessed 27-05-2022); CNHP Annual report 2021; Interview with representative of CNHP.

The German registry for Haemophilia contains granular patient information.

Local name: Deutsches Hämophilieregister (DHR)

Background

A well-developed national registry

- The registry collects medical data of patients with bleeding disorders from ca. 130 clinics across Germany.
- It was established in 2008, and developed and maintained by the Paul Ehrlich Institute (PEI).
- The registry is a collaboration between the patient organisations DHG and IGH, the medical society GHT, and the PEI.

Data are representative on a national scale

- All medical facilities treating patients with inherited bleeding disorders must participate in the registry.
- In total, the registry covered around 8,500 patients in 2019.

Electronic, separate data collection

- Patient-level data are collected electronically through manual registration to a web portal through physicians.
- The registry contains longitudinal data and is updated annually.
- The registry publishes annual reports and at least 5 scientific publications have relied on the registry.
- The registry cannot automatically be linked to other data sources.

Variables collected

Thorough information on the patient's health

- Patient data include demographics such as sex, age, height, weight, blood type, lab results, family medical history, and sick leave.
- No collection of socioeconomic variables, early retirement, lost income due to sick leave or quality of life scores.

Diagnosis, bleeding events, and treatments are reported at the patient level.

- The registry reports the patient's diagnosis (HA, HB, vWD, deficiency of coagulation factors*), its severity, joint scores, and all bleeding events (including localisation of bleeding, severity, and date of first treatment requiring bleeding).
- Historical diagnoses are not recorded.
- Treatment variables include start and end date of the therapy, medication (including dosage and frequency of all medications approved in Germany to treat haemophilia), gene therapy, and ITT. It also covers historical treatment (factor treatment before first treatment, requiring bleeding, date of first-factor treatment, change of medication before admission, and historical haemophilia medication).

Major adverse events such as inhibitor development are reported.

- Other medically relevant incidences can be added.

Governance structure

Data processing and sharing are regulated by the German Transfusion Act.

- A steering committee decides on whether and what data can be shared in line with the Transfusion Act.
- Sharing of patient-level data requires informed patient consent (opt-in programme).

Funding comes from PEI and public resources.

- The technical implementation and supervision of the registry are funded through PEI, supported by the Ministry of Health.

No collaboration with other registries

- However, aggregated data are shared annually with WFH.

Plans to synchronise data

- Centres plan to implement an interface to synchronise diaries from home therapy into the registry.

Source: Haschberger et al. (2008) - Aufbau des Deutschen Hämophilieregisters; Haschberger et al. (2009) - DHR – Ready for take-off; Haschberger at al. (2010) - Dokumentation in der Hämophilietherapie mit Unterstützung des Deutschen Hämophilieregisters Haemostaseologie ; Duda et al. (2020) - The German Hemophilia register: Growing with its Tasks; Annual reports and other documentation from the DHR https://www.pei.de/DE/regulation/melden/dhr/dhr-node.html/?cms_tabcounter=5 (accessed 27-05-2022). Additional information has been provided per e-mail by a representative of the DHR.
Note: *Coagulation factor deficiencies have only been collected since 2019.

The French registry collects granular patient information from across the country.

Local name: Réseau FranceCoag

Background

A well-developed national registry

- The FranceCoag network was implemented by the National Institute of Health and Medical Research in 2003 and was transferred to the Assistance Publique des Hôpitaux de Marseille in 2017.
- It stems from the National Therapeutic Monitoring of Hemophiliacs (SNH), created in 1994.

The number of patients is increasing over time.

- 34 centres across France contribute to the registry, ensuring almost exhaustive coverage.
- 12,843 patients were recorded in the registry in 2020.

Electronic, separate data collection

- Data are collected through a computer application.
- Treatment centres are encouraged to transmit data at least once per calendar year. Quarterly follow-ups are recommended for previously untreated patients.
- Annual reports have been published since 2018.
- At least 18 articles have relied on the registry.

Variables collected

Thorough information on the patient's health

- Patient data include demographics such as sex, age, weight, ethnicity, and family history of haemophilia.
- No collection of socioeconomic variables, sick leave and associated income loss, early retirement or quality of life scores.

Diagnosis and treatments are reported at the patient level.

- The registry reports the patient's current diagnosis (HA, HB, vWD, hereditary coagulant protein deficiencies) and its severity.
- Treatment variables include medication (number and dosage of injections), surgery, bypass products, and replacement therapy. The registry also collects data on the history of injections of substitute treatments on the date of inclusion.

Major adverse events are reported.

- Data are collected on inhibitors, HIV, HCV, and HBV.

Governance structure

Data processing and sharing are regulated by GDPR and the "Loi Informatiques et Libertés".

- For patient data to be shared, informed consent must be provided by the patient.
- Information about the purpose of the study, its nature, its recipients, and the patient's right to oppose consent is handed to the patient by the clinician.

Source: Public documentation from the FranceCoag Network https://francecoag.org/SiteWebPublic/html/documentsTele.html (accessed 27-05-2022).

The Irish Haemophilia registry is a FAIR compliant registry.

Local name: National Haemophilia Registry

Background

A well-developed national registry

- The Irish National Haemophilia Registry is a cloud-based registry established in 2005.
- It is interfaced with St. James's Hospital's electronic patient records.
- The registry can also be accessed by Children's Health Ireland at Crumlin, Cork University Hospital, and Galway University Hospital.

Data are representative on a national scale.

- The registry captures all patients with bleeding and clotting disorders.
- Approximately 6,200 patients are registered.
- In 2021, around 500 new diagnoses were added to the registry.

Electronic data collection

- Longitudinal patient-level data are collected automatically at the care unit by clinical staff (physicians, nurses, administration, hemovigilance, physiotherapists, dentists, social workers, and psychologists). Patients can add bleeding data via the Homescan app.
- The registry can be accessed by electronic medical records. Data can be linked manually to other medical records.
- Data are added in real-time.
- No annual reports are published.

Variables collected

Thorough information on the patient's health

- Patient data include demographics such as sex, age, race, and lab results.
- PRO are collected on paper after a change in medication.
- Currently no data on family medical history, sick leave and associated income loss, early retirement, or quality of life.

Diagnosis, bleeding events, and treatments are reported at the patient level.

- The registry reports patients' current and historic diagnosis (all bleeding and clotting disorders including carriers), joint scores, and all bleeding events.
- Treatment variables include clotting factor concentrate consumption including dosage (collected via the Homescan app). Historical treatment is also included.

All adverse events related to clotting factor concentrates (CFC)

- Reports side effects from CFC.
- Also records inhibitors and new coinfections.

Governance structure

Data processing and sharing are regulated by the Health Act 2004 and GDPR.

- The research and ethics committees of the hospital govern how data can be used for research.
- Processing and sharing of data require the patient's informed consent.
- Data cannot be used by industry.

Funding is provided by the hospital.

- No external funding.

No collaboration with other registries

- However, aggregated data are shared annually with WFH and EUHASS.

Plans to roll out a patient portal

- This will enable video consultations and enable patients to see their own records.

Source: Interview with a representative of the National Haemophilia System; Health Information and Quality Authority https://www.hiqa.ie/areas-we-work/health-information/data-collections/national-haemophilia-register (accessed 27-05-2022).

The UK's National Haemophilia Database is one of Europe's oldest registries for rare bleeding disorders.

Local name: National Haemophilia Database

Background

Historical national registry

- The registry was established in 1968 by the UK Haemophilia Centre Doctors' Organisation (UKHCDO).
- It is held by the NHS and managed by the UKHCDO.

A high number of patients in the registry

- In total, the registry comprised approximately 35,000 patients with HA, HB, vWD, and rarer bleeding disorders in 2021.

Electronic data collection

- Data are collected in local haemophilia centres that submit it to the registry every three months.
- Since 2008, some patients can enter information about their treatment and bleeding events through a home therapy reporting system called Haemtrack.
- Annual reports have been published since 2006.
- At least one publication is based on the registry.

Variables collected

Thorough information on the patient's health

- Patient data include demographics such as sex, age, ethnicity, weight, height, and family medical history.
- No collection of socioeconomic variables, early retirement, lost income due to sick leave or quality of life scores.
- PRO collected via Haemtrack.

Diagnosis, bleeding events, and treatments are reported at the patient level.

- The registry reports the patient's diagnosis (HA, HB, vWD, factor deficiencies, rarer bleeding disorders), its severity, joint scores, and all bleeding events (including localisation of bleeding, clinical bleeding history, bleeding pattern, and new bleeding episodes requiring haemostatic intervention).
- Treatment variables include brand and dosage of the product, surgery, treatment regimen (prophylactic/on-demand/ITI), and gene therapy.
- *Note that in the 1970s-1990s, only limited data were collected, such as diagnosis and severity, type and brand of CFC, and adverse events. The data coverage was significantly enhanced from 2005 onwards. The current list of variables became applicable in 2020.*

Various adverse events are reported in the registry.

- These include complications such as inhibitors, infections (including HIV, HBV, HCV), allergic reactions, death, intracranial haemorrhage, thrombotic events, COVID-19 infection, malignancy, neurological events, unexpected poor efficacy, and other events.

Governance structure

Data processing and sharing are regulated by the Data Protection Act and GDPR.

- Caldicott Principles and prevailing NHS information governance, guidance legislation, and good practice are also applicable.
- Allowed to use and transfer confidential data for (non-) research purposes due to Section 251 supports of the Health Research Authority.
- No patient consent is required, but patients can opt out.

Source: Public documentation from UKHCDO http://www.ukhcdo.org/nhd/ (accessed 27-05-2022).

The Italian National Registry of Congenital Coagulopathies reports key information about patients.

Local name: **Registro Nazionale Delle Coagulopatie Congenite (RNCC)**

Background

National registry built upon HIV infections

- Web-based platform initially developed in 1988 to monitor HIV infections.
- Since 2005, the registry has focused on congenital bleeding disorders.

Data are collected across Italy.

- 54 haemophilia treatment centres participate in the registry.
- 10,554 patients with HA, HB, vWD, and other congenital bleeding disorders were reported in 2018.

Separate data collection

- Treatment centres submitted longitudinal patient-level data to the Italian Association of Haemophilia Centres (AICE), which shares it with the Italian National Institute of Health (ISS). This data flow is no longer active since January 2022.
- A new mandatory system will be implemented between the regions (receiving data from centres) and ISS (currently in transition).
- Annual reports are published by the ISS.
- At least 5 publications have been based on the registry.

Variables collected

Basic information on the patient's health

- Patient data include demographics such as sex, age, region of residence, centre of reference, and weight.

Diagnosis and treatments are reported at the patient level.

- The registry reports the patient's diagnosis (HA, HB, vWD, other congenital factor defects, congenital platelet disorders), including severity and level of lacking factor. Historical diagnoses are also collected in the registry.
- Treatment variables include substitutive therapy dispensed at home (coagulation factors/bypassing agents/emicizumab). Drug prescriptions include brand, regimen (prophylaxis, on-demand, immune tolerance induction), dosage, units assigned in the therapeutic plan, and date of the treatment plan.
- No collection of data related to bleeding events.

Major adverse events such as inhibitors and coinfections are reported.

- These include current and historical inhibitor development and HIV and HCV.

Governance structure

GDPR guidelines governing data sharing are currently being. translated into Italian legislation

- Collection of data requires signed patient consent.
- Aggregated data can be shared for scientific research. No data sharing with industry.

No collaboration with other registries

- However, aggregated data are shared annually with WFH.

Funding of the registry

- The registry receives no funding.

Plans to link databases

- The aim is to link patients with inpatients, the Italian Pharmaceutical Performance Information System, and the Italian Health Card through an identification code.

Source: Hassan et al. (2017) - Italian registry of Congenital Bleeding Disorders; Abbonizio et al. (2016) - New data from the Italian National registry of Congenital Coagulopathies, 2016 Annual Survey; NRCC Annual report 2019 https://www.iss.it/rapporti-istisan/-/asset_publisher/Ga8fOpve0fNN/content/rapporto-istisan-21-15-registro-nazionale-coagulopatie-congenite.-rapporto-2019.-francesca-abbonizio-romano-arcieri-associazione-italiana-centri-emofilia-aice-e-adele-giampaolo (accessed 27-05-2022); E-mail statements from a representative of the registry from the ISS.

A strictly confidential registry monitors patients in Greece.

Background

A well-developed national registry

- The registry was established in 2007 and was initiated after several patients had been affected by coinfections.

Data are representative on a national scale.

- It registers all patients treated in the five Greek haemophilia centres.
- In total, 2,786 patients were recorded with HA, HB, vWD, and other bleeding disorders in 2020.

Electronic data collection

- Anonymised data from EMR is sent multiple times per year (updated all year round).
- Patients can be followed over time due to the longitudinal data structure.
- Data cannot be linked to other data sources.
- There are no annual reports or other publications based on the well-developed registry.

Variables collected

Thorough information on the patient's health

- Patient data include demographics such as sex, age, smoking status, haptoglobin values, cardiovascular diseases, lab values, and family medical history.
- PRO and quality of life measures are collected, but not systematically.
- No collection of socioeconomic variables, sick leave and associated income loss or early retirement.

Diagnosis, bleeding events, and treatments are reported at the patient level.

- The registry reports patients' current diagnosis (HA, HB, vWD, factor deficiencies, qualitative platelet disorders) and bleeding events.
- Historical diagnoses are not recorded.
- Treatment data cover factor concentrate consumption (plasma-derived and recombinant) including dosage.

Collection of various adverse events

- Collection of inhibitor development, coinfections, and any side effects are collected by physicians in the treatment centres.
- Side effects from home treatment are voluntarily reported.

Governance structure

Data cannot be used for research.

- Data sharing is governed by the Privacy Act of EMR and protective legislation in conjunction with disabilities for patients with coinfections.
- No data can be shared with third parties.

Funding is provided by the centres.

- No external funding is available.

Plans to update EMR

- Plans to update the national EMR system may provide additional data.
- The development of apps with interactive health care optimisation functions is constrained by the protective legislation in conjunction with disabilities for patients with coinfections.

Source: World Federation of Hemophilia (2021) – Annual Global Survey 2021; Interview with a representative of the National registry; Publication from the Greek Haemophilia Society https://www.yumpu.com/en/document/read/51063361/greece-ehc (accessed 30-05-2022).

Portugal has no registry, but a structure is in place to set it up.

Background

No registry for bleeding disorders

- All 5 treatment centres share aggregated data with the Ministry of Health.
- These 5 treatment centres cover almost the entire population.

Variables collected

The aggregated data collected by the ministry include basic variables.

- Number of patients, sex, age, diagnosis, treatment including dosage, surgery, emergency room visits, and side effects.

Governance structure

Data sharing is governed by national legislation.

- Data sharing requires patient consent.
- It is not prohibited by law to share data for scientific research purposes or with industry.

Huge potential for future development

- Treatment centres are starting to collect data on socioeconomic status, PRO, and QoL.
- Given the data flow between treatment centres and the Ministry of Health, a national registry could be set up.

Source: Interview with a representative from one of the treatment centres.

A newly developed national registry monitors patients in Romania.

Local name: **Registrul Persoanelor cu Hemofilie**

Background

The national registry was established very recently.

- The Romanian National Haemophilia Registry was launched only one year ago, in 2021.
- It was developed by the Romanian Society for Haematology together with Novo Nordisk.
- All four major treatment centres participate in the national registry.

Patient records are increasing.

- Currently, the registry covers only between 20% and 25% of the population (ca. 182 patients) as it is still in its early stages of development.
- The aim is to cover a majority of patients within the next two years by not only adding new patients but also adding data retrospectively.

Electronic, separate data collection

- Patient-level data are collected independently from medical charts by staff at the treatment centres (either PhD students or secretaries).

Several publications have relied on the registry.

- Annual reports and at least 4 publications have relied on the registry.
- Data can be linked to other data sources, but not systematically.

Variables collected

Basic information on the patient

- Patient data include demographics such as sex, age, lab data, and the patient's medical history.
- The registry does not collect family medical history, socioeconomic data, or quality of life.
- No collection of sick leave and associated income loss, early retirement, quality of life, or PRO.

Diagnosis, bleeding events, and treatments are reported at the patient level.

- Current and historical diagnoses include HA, HB. vWD, and all other coagulation disorders.
- All bleeding events are recorded, including the date of the bleeding and its location.
- Treatment variables include the exact treatment, including dosage of CFC, whether the treatment was followed, complications, and additional treatment in the presence of other comorbidities.

Adverse events

- All medium and severe adverse events are captured in the registry.

Governance structure

European law governs data processing and sharing.

- The EU GDPR regulates data collection and its usage.
- Data requests can be sent to the Romanian Society of Haematology, which decides what data can be shared.
- Sharing of patient-level data requires written consent from patients.

The registry receives external funding.

- Both the technical platform and the registrars are funded by Novo Nordisk and the Romanian Society of Haematology.
- **Collaborations exist within Romania.**
- The registry collaborated with the Romanian Society of Haematology and the Romanian Society of Paediatricians.
- Currently no collaboration exists with the pharma industry.

Future prospects to increase coverage

- Plans are in place to increase the number of patients.

Source: Interview with a representative from Romanian Hematology Society.

Several countries currently do not have a disease-specific registry in place or provide little public information.

Latvia

Latvia only has a rare disease registry.

- Due to the low number of patients with bleeding disorders (190 in 2020) and the high costs associated with developing a registry, only a general rare disease registry is in place.
- Information on patients' gender, age, region and disease ORPHA code can be requested from this registry.
- It is compiled by the Rare Disease Coordination Team.
- Statistics such as patient numbers shared with WFH are obtained from the rare disease registry.

Lithuania

Lacking information on the Lithuanian registry

- 504 patients were reported to the WFH in 2020.

Russia

Russia has a disease-specific registry

- The Russian Registry of Haematology belongs to the Russian Haemophilia Society.
- It covers patients with inherited bleeding disorders (HA, HB, vWD, and other bleeding disorders) and collects information on factor concentrate treatment.
- 10,879 patients were reported to the WFH in 2020.
- The registry is updated annually.

Source: World Federation of Hemophilia (2021) – Annual Global Survey 2021; Representative of the Latvia Hemophilia Society; Public documentation from Russian Hemophilia Society https://www.hemophilia.ru/english.html (accessed 30-05-2022).

Several countries currently do not have a disease-specific registry in place or provide little public information.

Croatia

No official registry in Croatia

- Several doctors have patient databases.
- An initiative to launch an official registry exists.

Slovakia

Lacking information on the Slovakian registry

- 2,739 patients were reported to the WFH in 2020.

Serbia

Historical national registry

- The National Registry of Patients with Inherited Bleeding Disorders was established in 1963.
- The Haemophilia Centre is in charge of the registry.
- 948 patients were reported to the WFH in 2020.
- Patient data include demographics such as age.
- The registry reports patients' diagnoses (HA, HB, vWD, and other rare bleeding disorders).
- Treatment variables include coagulation factor concentrates (FVIII, FIX, FVIII-vWF, rFVIIa, APCC).
- Major adverse events such as inhibitors are reported.
- Financing is provided by the Health Insurance Fund.

Source: World Federation of Hemophilia (2021) – Annual Global Survey 2021; E-amil statements of a representative of the Croatian Hemophilia Society; Mikovic et al. (2010) – Quality of Haemophilia Treatment in Serbia: National Haemophilia registry Report.


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APPENDIX

FAIR – Guidelines for data management and stewardship

FAIR (findable, accessible, interoperable, reusable) refers to four guiding principles to manage and steward data

1

Findable: Data need to be easily findable through unique, persistent identifiers and be provided with metadata that enable the creation of data catalogues.

2

Accessible: Refers to access protocol (URL), authorisation (standardised, machine-readable access request), and metadata longevity (ideally stored permanently).

3

Interoperable: Data integration by expressing (meta-)data in a formal, sharable, accessible, and applicable way (e.g., RDF) including links to publications and sources used.

4

Reusable: Data must be usable for new users and study purposes. This requires tracking of versions, names, and analytical tools.

FAIR principle compliance will improve the efficiency of biopharma R&D.

Applying FAIR principles makes data more accessible and machine-readable, allowing to automate processes through AI. This enables data reuse and scaling, which helps overcome long processes in the data value chain. Robotics and AI can improve efficiency by making the data ready for analysis and rapidly answering scientific queries.

This is associated with 4 key benefits:

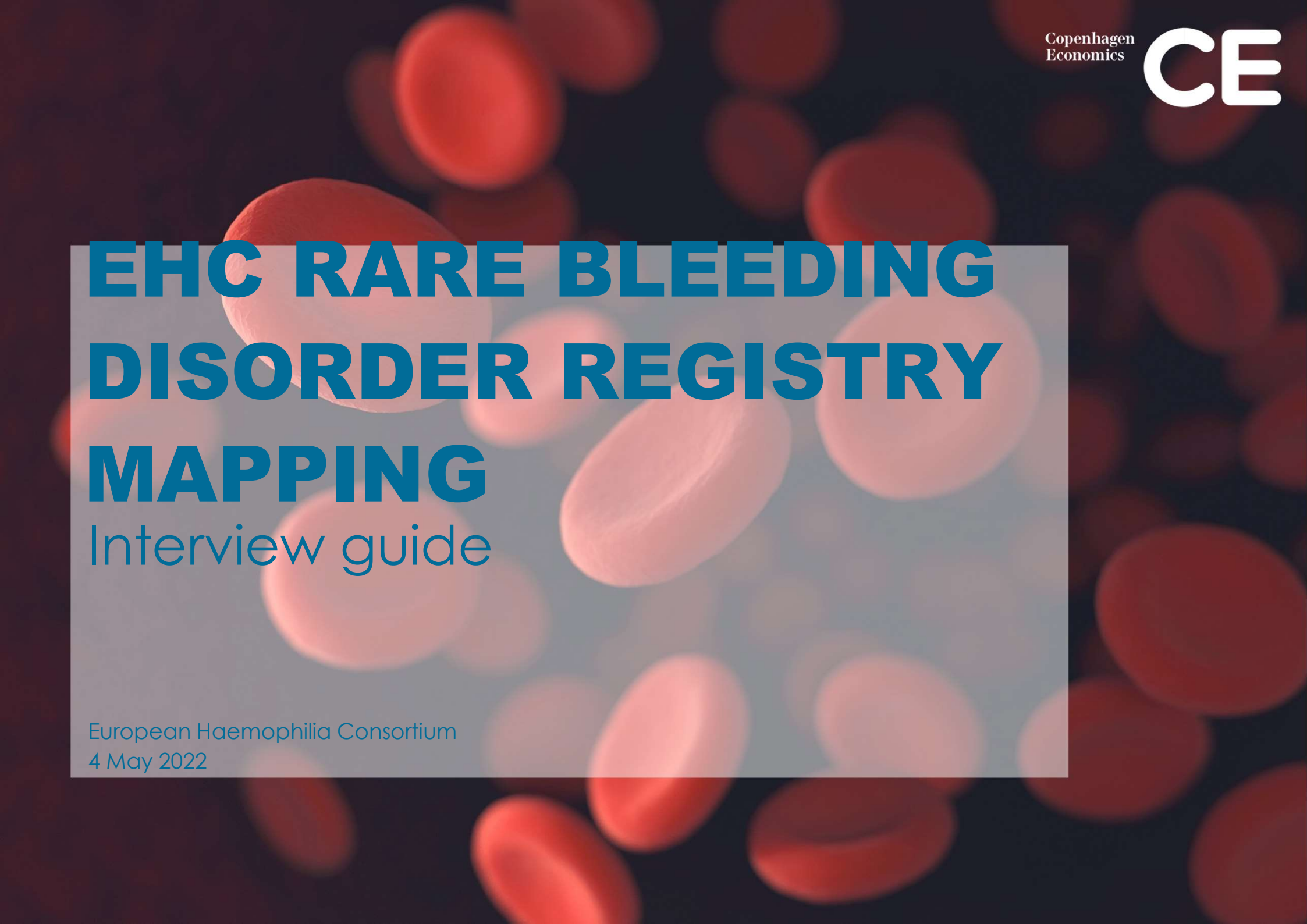
1. Accelerated innovation due to data availability for primary and secondary use.
2. Reduced drug discovery time due to shortened clinical trials.
3. Development of segmented and personalised drugs by exploiting real-world data.
4. Cross-institutional collaboration and sharing of data.

Overall, the time to generate value will be reduced, improving the productivity of drug research.

High costs associated with FAIR implementation hamper its adoption.

- Changes are required in standard operating procedures associated with financial investment.
- Responsibility is undefined (IT vs business).
- Collaboration is required between biopharmaceutical companies and technology supply companies (e.g., training, education and development programmes).
- The involvement of data stewards and all data stakeholders is required to achieve cultural change concerning data sharing.

Source: Wise et al. (2019) – Implementation and relevance of FAIR data principles in biopharmaceutical R&D.



Copenhagen Economics

EHC RARE BLEEDING DISORDER REGISTRY MAPPING

Interview guide

European Haemophilia Consortium

4 May 2022

The EHC is aiming to set up a governance structure for sharing of RWD.

- RWD have become important in developing and evaluating treatments. This is particularly important for those rare diseases where traditional randomised clinical trials are not possible.[1]
- Pragmatic clinical trials can provide an opportunity to generate evidence and are becoming more accepted by medical product agencies. [2]
- RWD from multiple countries have been used in post-approval safety studies to assess adverse events. [3]

- The EHC engaged Copenhagen Economics (CE) to perform a mapping of registries on rare bleeding disorders.
- The objective was to obtain an overview of which registries of rare bleeding disorders exist and to evaluate if and how data can be shared between registries.
- We performed the mapping of registries using a combination of desk research and interviews.

In light of the increasing need for RWD from multiple countries, the EHC is exploring the possibility of setting up a governance structure for collaboration between registries containing RWD on rare bleeding disorders.

Prior to the interviews, CE conducted desk research to collect information on potential registries to include in the governance structure. The purpose of the interviews was to deepen our knowledge of the registries and explore the basis for including them in the governance structure.

1) https://laegemiddelstyrelsen.dk/da/nyheder/2018/temaarrangement-om-big-data-og-medicin/~/media/1053CAFEB7B3413CBDDD3B6D10E07810.ashx ; 2) Aumfeld Andre E, Reynolds R, Caubel P, Azoulay L, Dreyer NA. Trial designs using real-world data: The changing landscape of the regulatory approval process. Pharmacoepidemiol Drug Saf. 2020 Oct;29(10):1201-1212.; 3) https://who-umc.org/

What is the background of the registry (1/2)?

Background:

- What is the background of the registry?
- What determines which clinics/centres contribute to the registry?
- When was the registry created?

Number of patients:

- How many patients are included?
- What is the number of new patients included each year?
- How has the number of included patients developed over the years?

Data collection:

- How are the data collected? Is it done systematically?
- Who can upload data (physicians, nurses, pharmacists, patients)?
- How often is the registry updated and what is the lag time?
- Are patient data collected longitudinally or cross-sectionally?
- Can data be linked to other data sources?

What is the background of the registry (2/2)?

Research and annual reports:

- How many publications have relied on the registry?
- Can it be used by industry?
- Are the data in alignment with FAIR?
- Do you publish an annual report?

Variables (1/3)

Diagnosis:

- What diagnoses do you collect data on?
- Do you collect data on historical diagnoses/events?
- Can carriers also be registered as mild patients?

Bleeding events:

- What data do you collect on bleeding events (timelines of input)?
- Do you collect data on historical bleeding events?
- If so, all events or just joint/muscle events?

Treatment:

- Which treatments do you collect data on?
- Do you collect current or historical treatments?
- Do you collect data on dosages?
  - CFC, TXA, DDAVP, hormonal therapy?
  - Do you collect usage on all or just CFC?
- Do you use GTIN standards (2D barcode) for data collection?

Variables (2/3)

Patient:

- Which patient characteristics do you collect?
  - Gender, date of birth, smoking status
  - Cardiovascular, HIV, HAV, HBV, HCV
  - GP bloods accessible
  - Labs access in the system
- Do you collect data on the family medical history (i.e., do you collect data on prevalence and incidence)?
- What socioeconomic variables do you collect?

Variables (3/3)

Adverse events:

- What adverse events do you collect?
  - Do you collect severe and mild events?

Sick leave/lost productivity and QoL:

- Do you collect data on sick leave?
- Do you collect data on early retirement?
- Do you collect data on income lost due to sick leave?
- Do you collect data on quality of life (generic QoL instrument)?
- Do you collect disease-specific PRO?

Clinic visit data:

- What data do you collect on visits?
- Do you collect data on length of stay (FAIR-ly collect)?
- Do you collect data on referrals?
- Do you collect data on emergency department visits?
- Can you record "Did not attend" data linkable to an individual?

Healthcare providers:

- Do you collect data from primary care providers (GPs)?
- Do you collect data on specialist care?
- Do you collect data on inpatient care?

Is there potential for participation in the governance structure?

Collaboration:

- Which collaborations have been performed with other registries?
  - 1) Industry
  - 2) Other national agencies (e.g., GP, home delivery)
- How have these collaborations been set up?
- Is there any formalised collaboration/information flow with insures/payers?

Funding:

- How is the registry funded?
  - Technical platforms vs people?

Legislation:

- Which legislation determines what and how data can be shared?
- What governs how data can be used for research and statistics?
- How is patient consent handled?

Future:

- Are there any concrete plans to develop the registry further?
  - For clinicians, patients, and the health system
- What plans do you have for setting up an interactive health care optimisation function?

EHC Registry Mapping

AUTHORS

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About Copenhagen Economics

Copenhagen Economics is one of the leading economics firms in Europe. Founded in 2000, we currently employ more than 90 staff operating from our offices in Copenhagen, Stockholm, Helsinki, and Brussels. The Global Competition Review (GCR) lists Copenhagen Economics among the Top-20 economic consultancies in the world and has done so since 2006.

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