Defining and Characterising a Toolkit for the Development of a Successful European Registry for Rare Liver Diseases.

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Abstract

Background:

A rare disease is defined by the European Health Commission as a disorder affecting less than 5/10,000 population. There are at least 20 rare liver diseases seen frequently in the adult and paediatric liver clinic, signifying that the hepatology community can be influential in developing such patient databases for registering patients with rare hepatic conditions. The aim of this systematic review was to 1) identify registries for rare liver diseases in Europe and 2) design a universal blueprint for the development of a registry for rare liver diseases by using lessons learnt from the already established European registries.

Methods:

We searched PubMed, google scholar and clinicaltrials.gov using the MESH terms “registries”, “database management systems”, “database” and the non-MESH terms “database$”, “registry”, “repository” and “repositories”. We only included studies in English from countries/consortia of the European Union (EU). Our literature search was performed in 2020.

Results:

We identified 37 registries for rare liver disease in Europe. Using information from the design of these registries we developed a blueprint for the development of a patient registry for rare liver diseases consisting of a theoretical, technical and maintenance phase.

Interpretation:

It is believed that rare diseases may affect as much as 6–8% of the EU population across its 28 member states. Here we have provided a toolkit for designing a registry for rare liver disease. Our article will complement the efforts of loco-regional, national and international groups seeking to establish robust systems for data collection and analysis for orphan liver diseases.

Key Points

This article sets out to:

- Provide a definition of rare liver diseases and disease registries
- Highlight the benefits of disease registration for rare liver diseases
- Review European efforts of disease registration for rare liver conditions using a systematic approach
- Provide a framework for building a successful disease registry
- Elaborate on strategies for optimum data quality and data management
- Recommend approaches for ensuring sustainability of disease registries for rare hepatic conditions.

Introduction

A rare disease (or an orphan disease) is defined by the European Health Commission as a disorder with prevalence <5/10,000 individuals. Different definitions exist for other populations (Table 1). A disease is defined as ultra-rare if less than one person per 100,000 people is affected(1). It has been estimated that there are between 5000-8000 rare diseases affecting 6-8% of the European Union (EU) population(2).

Unmet needs for rare diseases include diagnostic delays, lack of awareness and education, inequalities in the accessibility of care, fragmented delivery of care, poor availability of treatments and paucity in research initiatives(3). To address these gaps,

there have been strategy development and policy implementation around rare diseases including the EU(the Europlan project and Eurordis)(4, 5), the UK and the Royal College of GPs(RCGP)(6-9), Asia-Pacific(10-15), USA(16) and the World Health Organisation(WHO)(17).

The EU Committee of Experts on Rare Diseases (EUCERD) was set up with the purpose of encouraging the exchange of relevant experience, policies and practices in rare diseases among member states. One of the most important output activities of EUCERD is the provision of the basic governance and foundation in data collection and registration in rare diseases across 6 domains:

1. International operability
2. Sources of data
3. Collection of data
4. Good practices
5. Use of data for regulatory purposes
6. Sustainability

Despite this core framework, a comprehensive guideline of how to create an effective and contemporary registry for rare liver diseases does not exist. Rare liver diseases are often encountered in the hepatology clinic(Table 2). Their clinical management could be effectively improved through collective patient registration and subsequent data analysis.

What is a registry?

The term registry has been broadly used to cover both the act of recording of healthcare data as well as the collection of records. More specifically a registry can be defined as “an organised system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition or exposure, and that serves one or more predetermined scientific, clinical or policy purposes”(18). Clinical registries, are designed to capture data from a pre-defined population and tend to collect more data for each patient. An example is a hospital registry for intra-hepatic cholangiocarcinoma including all patients treated in the hospital. Population-based registries for the same malignancy hold data from patients who reside within a defined geographic region and may include patients who receive their treatments elsewhere. Population-based registries collect less data for each individual but generally, have higher ascertainment of cases.

The benefits of registries

Epidemiology & Public health:

Clinical registries are often used to register patients with rare disease. They are not usually capable of giving prevalence and incidence estimates of rare illnesses and are often biased as they are subjected to specialist centre bias, do not often include deceased patients (but this can be decided when considering the scope and information governance of the registry) and only include patients who have consented. However, they are excellent tools in elucidating the natural history of a rare diseases and facilitating the study of rare exposures and outcomes. They have the ability to improve the clinical interface by capturing data on individual patient journeys. Population-based registries (national and international) on the other hand may hold less granular data on individual patients but are more appropriate in studying rare and ultra-rare diseases including some of their epidemiological aspects because they focus more on numbers of patients and the chronological data around the diagnosis.

Clinical benefits:

The data within registries can be used to perform subgroup analysis for patients with rare diagnoses e.g. patients with Wilson Disease with stage 3 liver fibrosis. The data can be used to risk-stratify patients, identify high-risk patients requiring screening

and aid the development of decision support tools in order to promote proactive clinical management. Registries can also help to initiate, optimise and monitor pharmacotherapy.

Financial benefits

The long-term benefits of registries can help improve health economics even taking into account the initial set-up costs[22]. Electronic data extraction is often possible such as linking lab results directly to the registry. Moreover, they can identify gaps and inefficiencies in clinical care and improve the financial efficiency of health services. They can promote cost-savings by correct prescribing and can help achieve targets which may be financially incentivised. Data derived from patient registries can influence commissioning and therefore shape delivery of care.

Educational benefits

Disease registries can provide educational links including online evidence-based resources and guidelines. Registries can also be integral to care bundles such as the management of gastrointestinal bleeding(19).

Governance benefits

Health registries can improve data quality and facilitate audit and reporting of outcomes which can further improve local services, increase the quality of care delivered to patients and help to identify gaps in clinical pathways.

Research & audit benefits

Conducting clinical trials for rare liver diseases is challenging due to the small numbers of patients. Registries can provide large amounts of data to study orphan conditions especially when data is inputted from various recruiting sites. Candidate patients can be screened electronically for eligibility for inclusion into clinical trials. Furthermore, registries such as population-based registries, may promote and facilitate clinical audit. For example, the UK national lung cancer audit is carried out through the population-based national cancer registry.

Registries for rare diseases

Registries act as data repositories and help elucidate the natural history and patient outcomes for rare liver diseases. For example, survival outcomes in lysosomal storage diseases following enzyme replacement pharmacotherapy was first described using a patient registry(20).

The aim of this systematic review was to 1) identify registries for rare liver diseases in Europe and 2) design a universal blueprint for the development of a registry for rare liver diseases by using lessons learnt from the already established European registries.

Methods

We carried out a search to identify registries for liver conditions within the EU. Medical Subject Headings(MESH) and non-MESH criteria were used to search international academic databases(MEDLINE®/PubMed® and Cochrane), grey literature, clinicaltrials.gov and Google scholar. The MESH terms used included “registries”, “database management systems”, “database”. The non-MESH terms used were “database$”, “registry”, “repository” and “repositories”. We limited our search to articles published in English and on humans only. Our literature search was performed in 2020. Our approach follows the preferred reporting items for systematic review and meta-analysis (PRISMA) protocol. A total of 37 articles were included(Figure 1). We acknowledge that there are several registries for rare liver diseases; however, here we only included those which are non-interventional and with published outcomes and within the EU.

Results

From our search, we identified several registries with published outcomes as summarised in Table 3. Most of these registries included both patient and investigator-derived data.

Designing a registry for rare liver diseases

The design process can be divided into three stages; the theoretical, technical and maintenance phases(Table 4).

Aims and objectives

The theoretical phase begins by identifying the unmet needs the registry is expected to address. The goal of the registry should be defined early to inform the design process and outcome measures. A well-designed registry should be able to translate a clinical/academic question into measurable exposures and outcomes. Setting aims and objectives should take into account existing registries to avoid duplication. Many registries may have more than one purpose or rationale(21). For example, the main aim of the EuroWilson registry was to assess the feasibility of conducting randomised controlled trials for the treatment of Wilson's disease, while the UK-PBC registry aims to identify PBC patients including those not responding to ursodeoxycholic acid (UDCA), elucidate the molecular mechanisms that govern non-response and strengthen relationships between clinicians, the NHS, patients and industry. As registries develop, refinement of objectives could be considered to cover newly identified knowledge-gaps.

The commonest aims and objectives used in registry design for rare liver diseases are listed in Table 5.

Define target population & observation period

The definition of the target population will determine which patients are eligible for inclusion into the registry. Having very extensive and strict inclusion/exclusion criteria for registries may miss patients. It is generally preferred to have broader criteria in order to be able to redefine registry entries to identify previously unrecognised unmet needs and to accommodate any change in diagnostic criteria that can occur following improved understanding of the studied disease.

Part of this process involves consideration of whether data should be collected from deceased and paediatric patients as this will influence governance approvals required. Existing epidemiological data e.g. incidence and prevalence will help identify the expected numbers of cases for the registry, hence, guide decisions around planning, costing, IT infrastructure and workforce. If the registry is designed as part of a clinical trial, inclusion and exclusion criteria should be stated in the protocol. For example, D'Angolo *et al* used a cut-off of 20 liver cysts for inclusion into their polycystic liver disease registry study whilst the UK-AIH registry study excludes all patients who have HIV(22).

The duration of observation should also be considered at this stage as it can influence the design especially if the registry is set up as a clinical study. For example, a registry, which captures cross-sectional data on patients who received a liver transplantation, will be inherently different to a longitudinal registry study exploring the natural history and future outcomes of female patients who developed acute fatty liver of pregnancy.

Information, Research & Clinical governance

The design protocols for disease registries should include sections describing both the lawful basis of data collection for the registry as well as the process of accessing and extracting data from the database. Different countries have different bases for collecting data. For example, in England, the National Disease Registration Service collects rare disease patient data without consent under Section 251 of the NHS Act 2006 and the authority of the Health Service (Control of Patient Information) Regulations 2002 and in compliance with the General Data Protection Regulation (GDPR). Any data input/output should be governed by the principles that apply to all other health and social care research of the area(s) where the registry will be active (Table 4-theoretical phase). Any governance issues regarding the data sharing across countries should be identified early and discussed with the health research authority of each country. The scope of consent from patients should also be included in the registry protocol and laid out in detail in the research application if one is required. Consent should be such that it covers future relevant linkage opportunities or is set up as a reconsented model. Specific approaches to data including

pseudonymisation/anonymisation of records should be considered to protect patient identity, especially when extensive demographic data are not required to achieve the endpoints of the registry.

We recognise that this is particularly important for inherited rare diseases where there are data concerns relating to more than one member of the family. Oversight/steering committees, stakeholders and registry sponsors/funders, external experts and team-members with the relevant skillsets can all assist with adherence to governance policies and registry protocol.

Sponsorship and funding

The sustainability and efficient running of a registry are reliant on sufficient funding and sponsorship. It is therefore important to pilot a smaller-scale feasibility registry with fewer reporting sites. Registry funding can be sourced from various bodies including government organisations, non-profit disease foundations, patient groups, charitable foundations, private funds from philanthropists, industry and professional societies(18).

The European commission receives regular applications for funding support for rare diseases and its third Health Programme (covering the period from 2014-2020) offers support to the setting up rare disease registries as part of its operating framework(23). It is desirable for applications to consider collaborative efforts and ways of maintaining these and also to align with the recommendations of the High Level pharmaceutical forum for better access to orphan medicines(24). The European Association for the Study of the liver (EASL) also provides registry funding for liver diseases through its EASL registry data collection grant scheme. To date, it has awarded grants for the development of several orphan hepatic disease registries(25). Other organisations which also accept applications for registry funding include the UK's medical research council (MRC) and the UK National institute for Health Research (NIHR).

Establish the registry team

The workforce required for designing, running and maintaining the registry should be defined early on based on the objectives, size and funding of the registry. A multidisciplinary team approach is key to successful implementation and ongoing success of any registry.

The chief/principle investigator should have a continuous oversight of the process and work closely with project management to set realistic and achievable targets. Project managers with financial experience as well leadership and organisational skills are important for liaising with funding bodies and sponsors. A core requirement is for legal and information-governance expertise as well as a strong grounding in epidemiology, medical statistics and population-based studies is also extremely important. Registry operators with particular roles in data liaison should be considered in order to ensure the effective negotiation of data from data providers. Data entry should be undertaken by team members familiar with the core and desired datasets (see below section on data management system) to guarantee that minimum standards for quality assurance are met.

Identify stakeholders and set up wider collaboration

A registry may have one or more stakeholders which are people or organisations who have an interest in the research question the registry is trying to address. Stakeholders can be either primary or secondary(18). A primary stakeholder is responsible for the logistics of setting up the registry while a secondary stakeholder is identified as the party who will benefit from the data and the answers to the clinical endpoints of the registry. Commonest stakeholders include, clinicians, researchers, academic institutions, patients, public, community leaders, policy makers, professional societies, regulatory agencies and industry partners.

The importance of collaborations in the field of rare diseases where data is scarce and fragmented has already been highlighted. For example, in the EU, the OrphanXchange project has been set up by Orphanet in order to promote collaboration between academia and industry and was funded by EU's FP6 (6^{th} framework program). The establishment of registries sits deeply in the core of the project. Examples of successful large-scale registry collaborations on rare liver diseases include the

international PSC registry, the registry on Alpha1-antitrypsin deficiency, the European registry for liver disease in pregnancy and the European repository of patients with IgG_4-related disease all of which have been funded through the registry programme of the EASL(25).

Moreover, the EU Committee of Experts on Rare Diseases (EUCERD) was set up and ran between 2010-2013 with the purpose of encouraging the exchange of relevant experience, policies and practices in rare diseases among member states. By the end of its tenure, the committee had promoted cooperation across European countries as well as other countries with interest in rare diseases such as groups from Japan. Conclusions from this work include recognition that many data repositories are academic and that many rare diseases have more than one registry whilst others have none.

This has facilitated drafting a consensus across 6 domains namely international operability, sources of data, collection of data, good practices, use of data for regulatory purposes, and sustainability(Table 6)(26).

Registry design, data management and data quality

Recently, there have been significant efforts by the European Commission to address challenges in setting up registries for rare diseases especially around technical and regulatory matters including clinical and research governance. The EPIRARE(European Platform for Rare Disease Registries) project was funded to serve exactly this purpose when it was set up in 2013. More specifically, its 4 objectives are to:

1. Define the needs of the EU registries and databases on rare diseases
2. Identify key issues to prepare a legal basis
3. Agree on a Common data set and elaborate procedures for quality control
4. Agree on the Registry and Platform Scope, Governance and long-term sustainability

Though EPIRARE has provided the fundamental steps in setting the foundations for rare disease registries design, a comprehensive blueprint is not available.

Defining unmet needs

Timely definition of unmet needs and clarity of objectives and endpoints of the registry will guide the choice of data which will be classified as mandatory or core i.e. minimum dataset.

The importance of avoiding duplication of effort and developing wider collaborations has already been discussed. These are data which will address the critical questions which the registry is setting out to answer. Additional variables i.e. desired or non-core can be included which should also align with the overall objectives of the registry.

For example, the European liver transplant registry(ELTR) has been collecting prospective transplant data on patients with polycystic liver disease(PLD) including demographics, symptoms, disease complications, laboratory results, prior therapy, liver transplant complications, and patient/ graft outcomes(27). However, this registry was not designed to collect retrospective long-term data in order to address research questions around the natural history of PKD, quality of life, disease prognostication and patient risk-stratification. Drenth *et al* have set up an international registry of patients with PLD to serve exactly this gap not covered by ELTR (22, 28).

Data management system

Data management systems (DMS) serving registries for rare diseases must be dynamic, integrative, extendable, customisable and intuitive in order to serve the designed purpose and objectives. The choice of DMS depends on expertise and available funding. Ideally, the DMS should be able to derive data automatically from electronic patient records as soon as a patient is registered into the database. However, whilst this may be a desirable functionality for local registries, it may be not be feasible

for regional, national and international registries for many reasons including, heterogeneous data coding, multitude of patient workflow products, differences in ethics committee (or Institutional Review Boards equivalent in North America) standards across regions/borders, differences in local security protocols and the lack of electronic patient records. Therefore, the most resource-efficient way of achieving a common and shared data exchange could be a web-based model which can provide various database access levels. For example, the European Network for the Study of Cholangiocarcinoma (ENS-CCA) have achieved this by are using an established platform called REDcap (Research Electronic Data capture) to bring together data from 33 groups from 12 European countries, while other consortia such as UK-AIH use bespoke software solutions.

The role of a common shared platform that allows remote access and remote data entry for a rare liver disease is fundamental as it can shape the quality and integrity of data and format data in a standardised fashion. Once data fields are defined (e.g., mandatory *vs.* desired and content) data validation should be introduced at various checkpoints e.g. alpha vs. alphanumeric fields. Data validation is useful in ensuring that variables followed the expected format and prompting users to input missing data. Examples include typing extra decimal points and differences in lab units micromolsL-^{1} vs. mg/dl. As part of the registry's maintenance processes, regular data cleaning should also be undertaken for problems that might not be addressed by validation, such as logical inconsistencies. Data validation/integrity can be further improved through a multi-source approach to registration. This means that data should be collected from various independent sources when possible. An example is the UK's National Congenital Anomaly and Rare Disease Registration Service (NCARDRS) which collates, validates and registers data from various sources at local, regional and international level at various stages of the patients' journey. This approach enables NCARDRS to achieve the highest possible ascertainment and completeness of cases in the population(29).

Whilst having appropriately trained team members in data-entry, the use of a data dictionary is paramount in order to define each variable collected. This will clearly define the data terminology e.g. clarifying "negative" as test negative or test not done. Quick and effective data management can also be facilitated by having an intuitive and user-friendly DMS. Data quality is proportional to how straightforward the interface is. Whilst the use of case report forms-CRF(or eCRFs) has been necessary to standardise the data collected from each patient, this is less relevant as data is mined from large healthcare data sets and EPRs. Data liaison resource is required to assure that the data to the registry is mapped appropriately to the variables so that the incoming data meets the standardisation criteria.

Disease registries for rare diseases should be expandable and customisable to allow data linkage from different sources such as primary care, by providing options for integration with their databases(30). This is particularly important as many patients with rare liver diseases remain in primary care undiagnosed for a long time before they are referred for hepatology advice(31).

Data linkage with primary/tertiary care will allow a better understanding of the natural history of the rare liver disease being studied and will aid refinement of locoregional policy and referral pathways. One of the biggest challenges of achieving seamless data linkage is the heterogeneous coding with different classifications including Read codes(versions 2 and 3), Systematized Nomenclature of Medicine - Clinical Terms(SNOMED CT), Online Mendelian Inheritance in Man(OMIM), ICD-10 and Orpha numbers. Routinely collected health data is usually coded in ICD-10 which is not granular enough to identify cases. Notably, many rare diseases do not have an ICD-10 code. With the universal introduction of SNOMED-CT there will be a different problem – with over 1,000,000 codes, one cannot be sure that a comprehensive list of codes has been established so that cases can be retrieved from hospital data. It is not unusual to find rare diseases being misclassified in generalist registries. For example, our observational data identify several issues regarding rare liver diseases such as PBC, which is often coded as secondary biliary cholangitis, and different codes are used between primary and secondary care i.e. Read vs. ICD-10 (31). As part of the European strategy the EU has recommended that member states should ensure correct and traceable coding of rare diseases using the International Classification of Disease (ICD) in European health information systems. The EU is working closely with the WHO to ensure ICD-10 code revisions for rare liver diseases and future incorporation of all rare diseases into ICD-11 (32).Therefore, as data systems migrate towards shared coding schemes e.g. SNOMED-CT, automatic data mapping could be executed by the registry's DMS, acknowledging the issue of mapping from a less to more granular coding system.

As we move towards in the era of complete online data integration, it is particularly important to design registries for rare liver diseases with full online capabilities and capabilities of direct patient activation. This will allow the collection of patient-

reported outcome measures (PROMS) which have been considered in the context of rare diseases by several authors as well as quantitative data such as alcohol consumption and smoking history(33).

Some commercially-available DMS platforms such as Patient Knows Best (PKB) and Evergreen life allow patient-controlled medical records. We are not aware of these being considered for the management of rare liver disease.

Electronic surveys and questionnaires could feed directly into the DMS and patient-entered data could automatically update the data fields in the registry. One example is the UK-PBC 40 questionnaire which has been studied and validated in various settings and languages for PBC(34, 35). Delivering the questionnaire electronically to all PBC patients in the registry will facilitate earlier symptom management and will gauge response to pharmacological therapies. In their landmark study, Carbone *et al* also successfully collected self-reported data from patients with PBC utilising the PBC-40 questionnaire, the Epworth sleepiness scale, the orthostatic grading scale, the hospital anxiety and depression Scale, and the pruritus visual analogue scale. Patient-self reported data were cross-validated and found to be highly accurate(33). In a similar fashion, the DMS platform can be used to engage with relevant patient groups and charities.

Moreover, data from the DMS can help the development of decision support tools and provide reminders for clinical decision-making e.g. biannual ultrasound and alpha fetoprotein (AFP) screening for hepatocellular carcinoma (HCC) surveillance.

Finally, the DMS should integrate a data export mechanism for getting data out of the registry for research, audit and other purposes. The most popular formats include excel workbooks, comma separated text files, dBase files, XML data source and ODBC data source. The DMS should allow for options to export particular data fields rather than the registry as a whole. Applications for data from the registry should be made to the registry's project manager and should be discussed with the registry team. Some teams have established a data access review committee to review applications. Applications should be accompanied by a proposal outlining the scope of data use, and where relevant, should be supported by applications to relevant ethics committee (or Institutional Review Boards).

Quality control

The importance of standardisation, careful definition of data fields and field validation, user-friendliness of DMS and intuitiveness of data input has already been discussed above. We have also highlighted the usefulness of data cleaning as part of the registry's ongoing maintenance. Before the launch of a registry particularly when there is an anticipation of large volume of cases validation is required of existing data sources using data liaison resource i.e. data from a hospital's EPR and confirming the validity by linking to another data source. For example, a pilot run is recommended where 2-3 independent researchers input data for the same patients into the registry and areas of discrepancy are allowed to surface so that they can be resolved. A double-entry of 5-10% of all patients is considered to be an acceptable quality standard(36). The use of quality committees to audit registry records can also be considered especially for smaller cohorts such as rare liver diseases, but this option might be resource-heavy for larger registries for commoner conditions such as diabetes. Regular internal and external monitoring and auditing processes are required to ensure adherence to quality standards and information governance protocols. Data quality is also improved when the data is used for research and audit purposes. For this reason, it is vital to have feedback systems in place for data users.

Ensuring registry sustainability

Sustainability plans for the registry need to be defined in the early stages of the project design. These plans should be made with the close involvement of project managers, investigators, steering committee and various stakeholders. Sustainability plans will need to involve funders and sponsors as the value of grants and support will dictate the size of the registry and the timescale for data acquisition. Procedures around patient registration, consenting and participant retention (and loss to follow-up) will need to be outlined in the registry protocol. Exit strategies from the registry in the event of funding running out should be clearly discussed. Such strategies may include deletion of the data or discussion with research authorities for ways to contribute the mined data into other existing datasets of similar purpose.

It is not uncommon for incentives, including financial, to be considered for patients. The burden on participants will need to be outlined and weighed up against the benefits, and careful pilot testing of this should be undertaken prior to recruitment.

Whilst some aspects of participation in a registry may be burdensome for patients, benefits may include access to patient forums hosted by the DMS, access to clinical trial information as well as access to useful educational programs and tools. Many registries may be designed in such a way that consent is not required prior to data access. From our own experience, we have been able to set up such registries, however, we have provided our patients with the option of opting out if they did not wish for their data to be included. Ideally, and if patient numbers are manageable, patients should be consented for having their data included in a clinical registry. If the DMS is integrated with patient-controlled medical records, then enrolled participants can have access to results of their investigations and interact directly with their clinicians. The importance of data collected from PROMS on quality of life, clinical outcomes, social function and emotional status has been mentioned earlier. Whilst delivery of data from participants to the DMS can be laborious involving paper forms and multiple clinic visits the same process can become simple and fast in the digital era if participants are given a cross-platform access for data entry or data is extracted from existing patient records. The quality of participant engagement can be improved in some registries by having information or the DMS interface in various languages or culturally appropriate formats.

Feedback

Participant and team-member feedback is very important for the sustainability of registries for rare liver diseases. Engagement is encouraged where the team members reach out to participants with updates, information and newsletters and participants are also given a platform to express their opinions and concerns about the running of the registry. Telephone helplines, online patient forums and feedback to appropriate patient charities can be used to engage those on the registry or those considering registering or opting out. All sources of patient communication should be reviewed regularly by the project team and steering committee in order to improve services and participant experience. Measurable outcomes should be presented regularly at loco-regional, national and international meetings. This engagement will highlight the progressive work of the registry, can improve morale and could impact positively on patient engagement and retention.

Discussion

One of the biggest challenges in rare diseases is to identify pockets of expertise and existing data silos within a country/region as well as between international borders and link them. Collating these data remains particularly challenging due to the disparity in electronic systems and platforms and the heterogeneity in disease coding. Most rare diseases do not have ICD-10 codes and are often coded in Orpha codes. Therefore, routine data sources such as Hospital Episode Statistics (HES) cannot be used. Registries for rare liver diseases can have a multitude of benefits such as provision of high-quality patient care, research, commissioning, public health and patient empowerment to name a few. As part of the European initiative around rare diseases, several steps have been to improve expertise and information across European borders.

The Orphanet and the orphan drugs portal, funded by the EU's framework research programme (established 1997) provides a multilingual platform on rare diseases. The portal provides extensive information on registries and biobanks of all rare liver diseases and includes contact details for registry managers. It also provides information on Orphan drugs as well as information on centres of Excellence and expert laboratories, clinical trials and patient organisations/support networks in Europe. The importance of registries in rare liver disease remains paramount for evaluating patient outcomes especially in rare diseases where clinical trials may not be feasible due to low patient numbers. Whilst clinical trials may be the best way to define outcomes in a strictly defined population with a rare disease, registries remain more generalised and often capture a more comprehensive dataset which can be a closer representation to the real world. One important observation during the preparation of this work is the fact that several registries are established but have no published outcomes. It is therefore difficult to understand how these registries were launched and the actual datasets they hold. Sharing this experience would be invaluable in understanding the challenges that researches clinicians and developers face and appreciate strategies in overcoming them. This will also be useful for avoiding duplication of work including setting up multiple registries for the same rare disease. We would therefore encourage registry teams to consider publishing their experience in setting up their registries,

the scope of their work and the recognised unmet needs, the data fields they have included as well as the lessons learnt from the endeavour.

One of the major strengths of our paper is that it provides a novel blueprint/toolkit for designing a registry for rare liver disease. The framework builds on the strengths of already established registries which have been identified in our systematic review. Whilst we recognise the limitations of this paper is that it only includes registries with published outcomes, we are aware that several registries exist in various departments and institutions, these could not be captured comprehensively by a search if their outcomes have not been published.

Our systematic review will complement the efforts of the EASL “Registry Grants” scheme and ERN Rare liver. Collectively these programmes support the consortia groups dedicated to data gathering in liver disease by providing an operational framework for designing a comprehensive and integrated registry for orphan liver diseases and could facilitate the development of effective registries across Europe and beyond.

Declarations

Ethics approval and consent to participate

Not applicable. There was no ethics approval required for this work

Consent for publication

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Availability of data and materials

All data generated or analysed during this study are included in this published article [and its supplementary information files].

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Authors' contributions

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Tables

	Prevalence/10000 inhabitants	Persons concerned
EU	<5	<228,000
US	<7.5	<200,000
Japan	<4	<50,000
Australia	<1	<2000

Table 1: Definition of a rare disease in different parts of the world

ne	ICD-10 code		Name	ICD-10 code
gille syndrome	Q44.7	11	Nodular regenerative hyperplasia	K76.8
ha-1-antitrypsin deficiency	E88.0	12	HELLP syndrome	O14.2
onic autoimmune hepatitis	K75.4	13	Wilson disease	E83.0
ary atresia	Q44.2	14	Lysosomal acid lipase deficiency	E75.5
oli disease	Q44.6	15	Primary biliary cholangitis	K74.3
ycystic liver disease	Q44.6	16	Primary sclerosing cholangitis	K83.0
actosaemia	E74.2	17	IgG4-related sclerosing cholangitis	K83.0
n-HFE hemochromatosis	E83.1	18	Porphyria	E80.2
te fatty liver of pregnancy	O26.6	19	Reye syndrome	G93.7
ahepatic cholestasis of pregnancy	O26.6	20	Sarcoidosis	D86.0 D86.1 D86.2 D86.3 D86.8 D86.9

Table 2: Some of the commonest rare liver diseases often encountered in the hepatology and metabolic clinic according to http://www.orpha.net/ .

Abbreviations: HELLP= haemolysis, elevated liver enzymes and low platelet count (LP), ICD= International Classification of Diseases

Rare liver disease	Registry	Coordinator	Countries	Authors/reference	Patients identified
Polycystic liver disease	PLD registry	European (Netherlands)	4	Drenth *et al* (22)	725
	ELTR	European (France/Germany/UK)	27	Van Keimpema *et al* (27)	58
Primary biliary cholangitis (PBC)	UK-PBC	National (UK)	1	The UK-PBC consortium(37-39)	6040
	Globe PBC database	Global (Netherlands)	13	The Global PBC study group (40)	>6000
	French observatory of primary biliary cirrhosis	National (France)	1	Poupon *et al* (41)	N/A
Primary Sclerosing cholangitis (PSC)	UK-PSC	National (UK)	1	The UK-PSC consortium (42-44)	Nearly 2500
	IPSCSG	International (Netherlands)	22	Boonstra *et al* (45, 46)	992
	French observatory of primitive sclerosing cholangitis	National (France)	1	Chazouillères *et al* (47)	150
Autoimmune hepatitis	UK-AIH	National (UK)	1	The UK-AIH consortium(48, 49)	1616
	ELTR	European (France/Germany/UK)	27	Schramm *et al* (50)	827
Wilson disease	Eurowilson	European (Italy)	22	Eurowilson consortium (51, 52)	546
	Bulgarian national registry of patients with Wilson disease	National (Bulgaria)	1	Miteva *et al* (53)	162
	GeNeMove: German database for Wilson disease	National (Germany)	1	Oertel *et al* (54)	N/A
Acute liver failure	ELTR	European (France/Germany/UK)	27	Germani *et al(55)*	4903
	EMO-ALF STUDY	European (UK)	N/I	Simpson *et al* (56)	N/I
Erythropoietic porphyrias	ELTR	European (France/Germany/UK)	27	Wahlin *et al* (57)	31
	European Porphyria Registry (EPR)	European (Norway)	11	Elder *et al* (58)	335
	Norwegian Porphyria Registry	National (Norway)	1	Mykletun *at al* (59)	680
Caroli's disease	ELTR	European (France/Germany/UK)	27	De Kerckhove *et al* (60)	110
HHT	ELTR	European (France/Germany/UK)	27	Lerut *et al* (61)	40
Hepatitis delta	Hepatitis Delta Registry and Research Network	Global (Germany)	10	Wedemeyer*et et al* (62)	Aim 1000
Autoimmune Pancreatitis	IgG4-RD Registry	European (UK)	1	Barnes *et al* (63)	500
Vascular liver disease	VALDIG registry	Global (France)	19	Plessier *et al* (64)	N/I
	REHEVASC: Spanish registry for hepatic vascular diseases	National (Spain)	1	The CIBEREHD group (65)	>450
Alpha-1-antitrypsin deficiency	Alpha 1 International Registry (AIR)	Global (UK)	27	N/I	5000
	Portuguese registry for alpha-1 antitrypsin deficiency	National (Portugal)	1	Meira *et al* (66)	1684
Biliary Atresia	EBAR registry	Global (Germany)	22	Petersen *et al* (67)	514
	French observatory of biliary atresia	National (France)	1	Serinet *et al* (68)	743
	Romanian biliary atresia registry	National (Romania)	1	Sabetay *et al* (69)	N/I
Haemochromatosis (rare forms including aceruloplasminaemia)	French registry of Iron overload genetic rare diseases, non-related to the HFE gene	National (France)	1	Bardou-Jacquet *et al* (70)	1085
Cholangiocarcinoma	The European Network for the Study of Cholangiocarcinoma (ENS-CCA)	European	15	Banales *et al* (71)	1820
Hepatic Angiosarcoma	The British hepatic angiosarcoma register	National (UK)	1	Baxter *et al* (72)	88

Table 3: Examples of registries for rare liver diseases. Abbreviations: N/I=not identified, PLD=polycystic liver disease, ELTR=European liver transplant registry, PBC=primary biliary cholangitis (formerly cirrhosis), PSC=primary sclerosing cholangitis, IPSCSG=international primary sclerosing cholangitis group, AIH=autoimmune hepatitis, EMO-ALF=European study of the epidemiology, management and outcome of acute liver failure, IgG4-RD= Immunoglobulin G4 related disease, VALDIG=vascular liver disease group, REHEVASC=Registro de Enfermedades Hepáticas Vasculares, EBAR=European biliary atresia registry. The table does not include isolated regional general rare disease registries and cancer registries e.g. the international perihilar cholangiocarcinoma international registry.

Theoretical phase	**1**	**Aims, objectives**	
	2	Define registry population and observation period	Disease ontology and case eligibility. Consider geographical/residence inclusion criteria
	3	Information, research and clinical governance	1. Safety & wellbeing of patients and investigators 2. Competence and adequate qualifications of registry team 3. Appropriate scientific and ethical conduct according to national research governance policies 4. Peer-reviewed registry proposal 5. Patient, service user and public involvement 6. Integrity, quality and transparency of data collection and maintenance 7. Protocol to clearly explain the design of the registry 8. Legality of the registry e.g., compliance with the EU Directive 45/96 9. Benefits and risks to patients should be identified and stated 10. Ethics approval from bodies overseeing research governance e.g., Health Research Authority (HRA) in the UK and Institutional review board (IRB) in the US. 11. Information about the registry to be made publicly available 12. Accessible findings 13. Respect autonomy of participants and afford respect and choice in relation to consent or refusal of consent. Develop robust opt-out mechanisms. 14. Indemnity and liability insurance 15. Respect for privacy by practising strict information governance rules and ensuring safe data-keeping 16. Compliance with all regulatory processes
	4	Sponsorship & Funding	
	5	Establish the registry team	Recognise areas of expertise of team members and assign distinct roles
	6	Identify stakeholders & set up collaborations	Seek locoregional, national and international collaborations
Technical phase	7	Registry design and data quality	1. Define data fields and set core/mandatory (minimum dataset) and desired components 2. Build in data validation checkpoints 3. Is there a need for patient-identifiable information? 4. Explore feasibility of data linkage e.g., primary/tertiary care 5. Will the registry benefit from patient self-reported outcomes? 6. Engage with patients, the public and relevant charities 7. Is the registry designed for clinical decision-making?
	8	Data management	1. Choose an appropriate data management system (DMS) 2. User-friendly interface for quick data entry 3. Multilevel user access 4. Enable remote access and data entry 5. Develop a strategy for handling missing data 6. Consider accessibility to data; how can one apply for access and who reviews the application and process for releasing data when appropriate to do so
Maintenance phase	9	Ensure sustainability	1. Form a steering committee/advisory group 2. Regular consultations with stakeholders 3. Presentation of outcomes in local, regional and international meetings 4. Long-term funding 5. Continental/international data feeding into larger datasets 6. Consider incentives for participants

Table 4: Essential components for creating a successful and sustainable registry in rare diseases

Epidemiology estimates of rare liver disease e.g. prevalence and incidence
Natural history; birth-to-death
Validate established diagnostic parameters including diagnostic scoring systems
Understand treatment availability and disparity of care in various settings e.g. between regions/countries
Treatment monitoring and long-term therapeutic efficacy
Treatment experience and health safety e.g. teratogenicity
Understand reasons for loss of response to treatment
Elucidate survival outcomes
Assessing quality of life
Prognostication and development of risk-scoring systems
Establishing a specimen biorepository (biobank)
Assess the feasibility of conducting loco-regional, national and international clinical trials
Recruitment into clinical trials
Demonstrate the performance of drugs or devices in the real world
Benchmark clinical performance and assess adherence to clinical guidelines and protocols
Assessing health inequalities across different variables e.g., indices of multiple deprivation

Table 5: Commonest aims and objectives for rare liver disease registries.

	Domain	Section	Additional comments
1	internationally interoperable data collection and registration	Coding (OMIM, Orpha, SNOMED CT and ICD-10 codes)	Include dominant coding systems and the ability to map from OMIM or Orpha codes to ICD-10 and SNOMED CT.
		Minimum common data set in line with global initiatives	
		Avoid duplication and support cross-border healthcare	Consider European patient identifiers to link data
2	Consider all sources of data	Clear objectives	
		Centres of expertise and other centres should contribute	
		Utilise all sources of electronic healthcare records	
		Collect data according to national strategy on rare diseases	
		Data collection platform should incorporate direct data collection from patients	
3	Data should be used for research and the benefit of public health	Support development of health care policy	Local, Regional, National, International
		Clinical & Epidemiological research	
		Monitoring of care provision and therapy	Including therapeutic intervention and off-label use of approved drugs
		Inform the feasibility for multicentre and multinational clinical trials	
		Encourage data pooling	Including international pooling
		Make data accessible to researchers and policymakers	Information and research governance standards to be observed
		Safeguard the release and publication of data	
4	Adherence to good clinical practice guidelines	Involvement of stakeholders in the design, analysis and governance	Patients, Public, Policymakers, Regulatory agency, Researchers, Clinicians, (industry)
		Set up steering committee/advisory group	
		Define sustainability and exit strategy	
		Extend the scope of consent to a European/international context	Additional consenting steps may be necessary even for patients who have already consented to be registered
		Include a feedback mechanism	For clinicians and patients
5	Adaptable data collection	Accommodate disease monitoring and therapeutic interventions	
		Consider collection of data for regulatory purposes	
		Decide early on the type of registry required or whether more than one registry exists	
6	Sustainability	Ensure adequacy of financial support	
		Consider public-private partnerships	
		Establish exit strategies	“fate” of data in the event of registry termination

Table 6*:* European Union Committee of Experts on Rare Diseases (EUCERD) *has described six domains governing data collection and registration for patients with rare diseases in Europe.*

Figures

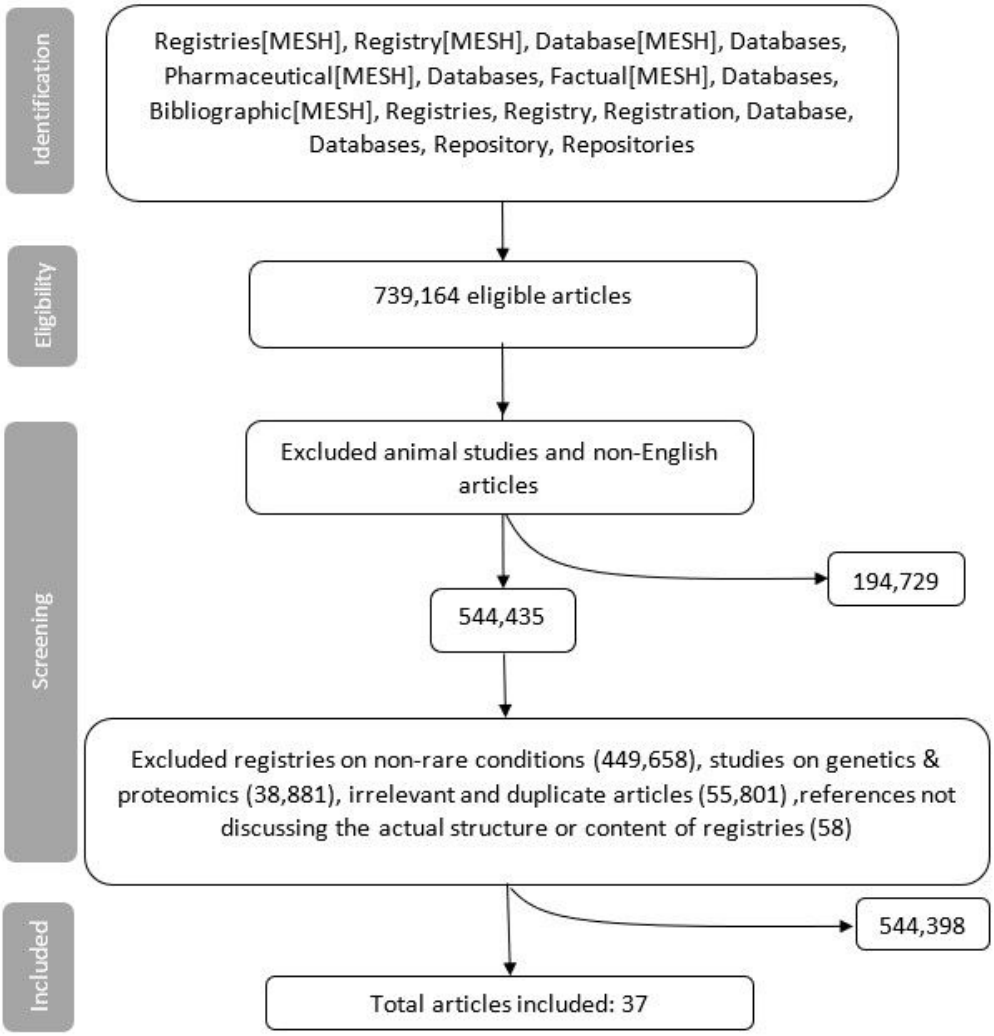

Figure 1

PRISMA flow chart of included studies