Review Article

Establishing a cardiology registry: navigating quality and regulatory challenges with a focus on congenital heart disease

Robert David Pittrow[1]^, Oliver Dewald[1], Frank Harig[1], Ann-Sophie Kaemmerer-Suleiman[1], Mathieu Suleiman[1], Leonard Bernhard Pittrow[1], Stephan Achenbach[2], Annika Freiberger[3], Sebastian Freilinger[3], Benjamin Alexander Pittrow[3], Renate Kaulitz[4], Harald Kaemmerer[3]

[1]Department of Cardiac Surgery, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; [2]Department of Medicine 2-Cardiology and Angiology, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany; [3]International Center for Adults With Congenital Heart Disease, Clinic for Congenital Heart Disease and Pediatric Cardiology, German Heart Center Munich, Technical University Munich, München, Germany; [4]Universitätsklinikum Tübingen, Pädiatrische Kardiologie, Tübingen, Germany

Contributions: (I) Conception and design: RD Pittrow, H Kaemmerer, F Harig, O Dewald; (II) Administrative support: A Freiberger, BA Pittrow, LB Pittrow, AS Kaemmerer-Suleiman, R Kaulitz; (III) Provision of study materials or patients: None; (IV) Collection and assembly of data: BA Pittrow, M Suleiman, S Freilinger; (V) Data analysis and interpretation: LB Pittrow, S Achenbach, RD Pittrow, H Kaemmerer, F Harig, O Dewald; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

Correspondence to: Robert David Pittrow, MD. Department of Cardiac Surgery, University Hospital Erlangen, Friedrich-Alexander-Universität Erlangen-Nürnberg, Krankenhausstr. 12, 91054 Erlangen, Germany. Email: robert.pittrow@uk-erlangen.de.

Abstract: Registries have become pivotal in medical research, offering a robust foundation for understanding disease incidence, treatment patterns, and patient outcomes across diverse populations. By aggregating real-world data (RWD), registries provide invaluable insights into real-world evidence (RWE), shaping clinical guidelines, healthcare policies, and regulatory decisions. Their widespread acceptance underscores their scientific validity and their role in driving evidence-based medicine, ultimately improving healthcare outcomes. In cardiology, particularly within the specialized field of congenital heart disease (CHD), national and international registries have emerged as indispensable tools. They enable the systematic collection of data on patient demographics, disease progression, therapeutic interventions, and long-term outcomes. These datasets support a range of purposes, including observational studies, quality improvement initiatives, and regulatory assessments of medical devices or pharmaceuticals. Establishing a high-quality registry requires meticulous planning and adherence to established guidelines. Professional organizations, such as the European Society of Cardiology (ESC) and the American Heart Association (AHA), offer detailed guidance documents for setting up and managing registries. Additionally, various checklists and frameworks exist to evaluate and ensure registry quality, aiding researchers in optimizing data reliability and utility. With advancements in digital health, the potential of electronic health records (EHRs) to complement or replace traditional registries is increasingly explored. EHRs offer a dynamic, real-time data collection mechanism, reducing redundancy and operational costs while maintaining data accuracy. However, considerations around interoperability, data privacy, and standardization remain critical in leveraging EHRs for registry purposes.

Keywords: Review; registry; cardiology; congenital heart disease (CHD); observational study

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^ ORCID: 0009-0000-2673-4772.

Introduction

The growing importance of registries is underscored by their frequent citation in high-impact medical journals and the large number of related studies indexed in Medline. Currently (October 2024), a search for the term 'registry' in Medline yields 267,000 hits [when limited to cardiology 25,000 hits, when limited to congenital heart disease (CHD) 1,390 hits], with a sharp increase in recent years. A systematic review conducted in 2020 found that over the past 40 years, 155 national cardiac registries were established, encompassing 72 million patients in 49 countries. Enrollment was based on procedures in 60% and on diseases in 40%.The review highlighted that data management practices and quality varied significantly across these registries (1).

Adults with congenital heart disease (ACHD) represent a growing field within cardiology, as advancements in congenital cardiology and cardiac surgery have increased survival rates into adulthood (2). The management of CHD poses unique challenges due to the complexity and variability of CHD, necessitating comprehensive data to inform clinical practice and research (3-5). In this context, clinical registries are invaluable providing a structured approach to collect, analyze, and disseminate data specific to ACHD.

Despite these advancements, the quantity and quality of clinical studies in this area is unsatisfactory, particularly with regard to pharmacotherapy. This is partly because the presence of CHD often is a contraindication for participation in clinical trials (6,7). Furthermore, the pharmaceutical industry's engagement with this complex area of cardiology has been limited, resulting in a dearth of targeted research and therapeutic innovation (4).

Given the relative rarity of some CHD, international collaboration is crucial to support the generalizability of research findings and the development of best practices for ACHD management (8,9).

The purpose of this manuscript is to provide insights into the quality and regulatory aspects involved in establishing cardiac registries, and to highlight their potential for advancing clinical research, improving patient care, and supporting regulatory decision-making. The manuscript offers a high-level overview of the frameworks and methodologies employed by organizations such as the American Heart Association (AHA) and the European Society of Cardiology (ESC) to establish and maintain cardiology registries. Additionally, it explores relevant aspects that may arise when registry data is utilized in a regulatory context.

AHA and ESC approach to registries

The AHA, in its policy statement on the applications of existing and future registries, has defined the term "clinical registry" as "observational database of a clinical condition, procedure, therapy, or population in which there are often no registry-mandated approaches to therapy and relatively few inclusion or exclusion criteria" (10).

Clinical registries are designed to collect data that represent real-world clinical practices across large groups of patients. They are not intended to replace traditional randomized controlled trials; instead, they serve as complementary methods, each offering distinct benefits and limitations. Clinical registries typically contain more than just claims or administrative data, though they can be connected to these data sources. AHA uses three main classifications of clinical registries, namely registries (I) based on the patient population, including procedure/therapy/encounter-based, (II) disease-based registries, and (III) population-based registries (10).

The AHA policy statement address five main areas, namely (I) epidemiological research, offering data on disease incidence and prevalence; (II) clinical research, providing real-life data on treatment patterns, outcomes, and quality of care; (III) comparative analysis across different settings and countries; (IV) monitoring adherence to clinical guidelines and ensuring quality control; (V) conducting economic evaluations of healthcare interventions (10).

The ESC has long utilized registries to gather comprehensive real-world data (RWD) on cardiovascular diseases, facilitating the evaluation of clinical practices, treatment outcomes, and adherence to guidelines across Europe. In 2009, the ESC launched the EURObservational Research Programme (EORP) to enhance understanding of medical practices through well-structured observational studies (11). The EORP has addressed 15 different cardiac topics across 34 registries, involving 102 countries worldwide, with an average of 27 countries participating in each registry. Overall, over 4,000 centers have contributed to EORP registries, enrolling more than 180,000 patients to date (12). The three types of registries supported by ESC in the clinical cardiology field are (I) common diseases [heart failure, atrial fibrillation, ST-segment elevation myocardial infarction (STEMI), non-ST-segment elevation myocardial infarction (NSTEMI)], (II) intervention (e.g.,

atrial fibrillation ablation, valve durability), and (III) rare conditions and diseases (e.g., pregnancy and cardiac diseases). The program led to hundreds of publications. Moving forward, the ESC plans to enhance these registries—in collaboration with the European Medicines Agency (EMA) (13)—with advanced digital tools and big data analytics, supporting high-quality research and promoting person-centered care and sustainability in cardiovascular medicine (14).

In Germany, both the German Society of Cardiology (DGK) and the German Society of Thoracic and Cardiovascular Surgery (DGTHG) have initiated a number of pivotal registries (15,16), including the German Aortic Valve Registry (GARY) (17), the German Registry for acute aortic dissection type A (GERAADA) (18), and many other projects.

Also, for ACHD, the establishment of disease registries is essential to optimize the understanding and improvement of the management. A few national and international long-term registries have been developed, such as COMPERA-CHD (19), ARTORIA-R (20), or the new PATHFINDER registry (21), which provide large datasets on pulmonary hypertension or heart failure in ACHD. Such long-term data are particularly important for understanding disease progression, treatment efficacy, and the impact of comorbidities. For example, insights from the COMPERA-CHD registry have contributed to improved treatment protocols and outcomes for ACHD with pulmonary hypertension (19).

Regulatory perspectives

RWD encompasses data related to patient health status and/or the delivery of healthcare, routinely collected from various sources such as electronic health records (EHRs), medical claims, product or disease registries, and digital health technologies. Real-world evidence (RWE) refers to the clinical evidence regarding the usage and potential benefits or risks of a medical product, derived from the analysis of RWD (22,23).

Regulatory bodies like the Food and Drug Administration (FDA) in the United States and the EMA in the European Union emphasize the increasing importance of RWD and RWE derived from various study designs, including randomized trials, large simple trials, pragmatic trials, and observational studies (prospective and/or retrospective) (24,25).

The FDA has a longstanding practice of utilizing RWD and RWE to monitor and evaluate the safety of approved drugs (26). Although historically RWE has also supported assessments of drug effectiveness, its application in this context has been more limited. FDA officers have emphasized that RWE is not limited to observational research. It can also be generated in the context of randomized interventional studies or non-randomized interventional studies (23).

Recent advances in the availability and analytical methods of RWD have significantly improved the potential to generate robust RWE, and thereby supporting FDA regulatory decisions. The FDA is committed to fully utilizing fit-for-purpose RWD to generate RWE, which will drive the development of therapeutic products and reinforce regulatory oversight throughout the lifecycle of medical products (26). The 21st Century Cures Act of 2016 aims to accelerate medical product development and expedite the delivery of new innovations and advancements to patients more efficiently (27). In response, the FDA established a framework in 2018 for evaluating the potential use of RWE to support the approval of new indications for drugs and biological products already approved and to fulfill post-approval study requirements for these drugs. Multiple FDA centers integrate RWD and RWE into their daily operations based on the nature of their work and the scope of their regulatory responsibilities (26).

In 2021, the FDA published four guidance documents focused on the use of RWD and RWE in regulatory decision-making. These documents provide comprehensive guidance on several critical aspects: how to select data from existing data sources, how to use existing registries for regulatory decisions, how to apply data standards, and an overview on FDA's expectations on non-interventional studies (23). In 2023, the Agency published "Considerations for the Use of Real-World Data and Real-World Evidence To Support Regulatory Decision-Making for Drug and Biological Products" (28).

At the same time, the EMA has increased its activities on RWE. While RWD/RWE has long contributed to safety monitoring and disease epidemiology throughout the life cycle of medicines, it is increasingly being used to demonstrate efficacy (29,30). Importantly, in collaboration with the European Medicines Regulatory Network, EMA set up a dedicated RWE team with the task to facilitate regulatory evaluations. They established the coordination centre "Data Analysis and Real World Interrogation Network" (DARWIN EU®) with the aim to provide timely and reliable evidence on the use, safety and effectiveness of

medicines, including vaccines, from real world healthcare databases across the EU (31). DARWIN EU supports regulatory decision-making by establishing and expanding a catalogue of observational data sources for use in medicines regulation; providing a source of high-quality, validated real world data on the uses, safety and efficacy of medicines; addressing specific questions by carrying out high-quality, non-interventional studies, including developing scientific protocols, interrogating relevant data sources and interpreting and reporting study results. The development of DARWIN EU is included in the EMA-HMA Big Data Steering Group Workplan and is a key component of the European Medicines Agencies Network Strategy through 2025. The vision of DARWIN EU is to give EMA and national competent authorities in EU Member States access to valid and trustworthy RWE, for example on diseases, patient populations, and the use, safety and effectiveness of medicines, including vaccines, throughout the lifecycle of a medicinal product (31).

The EMA has also published the Guideline on registry-based studies (32). It is based on a discussion paper on methodological and operational aspects of patient registries, which received extensive public consultation feedback from 68 stakeholder organizations. The final guidance incorporates insights from EMA's Committee for Medicinal Products for Human Use qualification opinions for two registry networks and input from five workshops on specific patient registries organized by the Agency (32). The document outlines the methodological, regulatory, and operational aspects of using registry-based studies for regulatory decision-making. It aims to assist in the definition of study populations, the design of study protocols, and provides guidance on data collection, quality management, and analysis to ensure high quality evidence. It focuses on disease or condition registries for the benefit-risk assessment of medicines, highlighting methodological differences between study types. It also includes an appendix on best practices for setting up and managing patient registries for regulatory purposes.

Overall, this guideline supports a more data-driven regulation of medicines, aligning with the Big Data Steering Group Workplan and the Network Strategy to 2025 (33).

Overview of guidelines on registries

Table 1 provides an overview of the guidelines issued by various professional bodies, regulatory agencies or journal editors. Initially, the guidelines were quite brief and focused on paper-based studies. Over time, the updates have become more comprehensive.

In general, a practical approach is to consider local guidelines first (e.g., GEP for Germany), followed by international guidelines such as good pharmacoepidemiology practices (GPP) (35), International Society for Pharmacoeconomics and Outcomes Research (ISPOR) (36), and European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (EnCePP) (40). For drug safety studies [Post-Authorization Safety Study (PASS)], whether required by the EMA or not, the EnCePP guidelines (40) should be the starting point. Registries involving centres in the USA should follow to the registry guidelines of Agency for Healthcare Research and Quality (AHRQ) (38), a sister agency to the FDA within the Department of Health and Human Services (41). In any case, it is essential to consult the STROBE guidelines (39), as many journals require compliance with STROBE for publication (42).

Quality indicators

The importance of quality indicators in registry studies cannot be overstated, as they play a critical role in ensuring that such studies meet high-quality standards and produce reliable and valid data. Quality indicators provide a framework for systematic and transparent processes, fostering trust and consistency in the use of registry data for clinical, research, and regulatory purposes.

To support these efforts, several institutions have developed detailed checklists and tools designed to assess and ensure the quality of registries (*Table 2*). These checklists are often comprehensive and cover a wide range of criteria. For instance, the quality criteria list developed by the Institute for Quality and Efficiency in Health Care (IQWiG) includes 47 different items that address aspects such as data collection methods, governance structures, and analytical rigor (46). These criteria not only help maintain the integrity of registry data but also guide researchers in establishing robust registries from the outset.

One notable tool is the Registry Evaluation and Quality Standards Tool (REQueST), developed by the European Network for Health Technology Assessment (EUnetHTA) under Joint Action 3. This tool is specifically designed to support Health Technology Assessment (HTA) organizations, evidence developers, and other stakeholders. REQueST provides a structured approach to evaluating the quality of registries and ensuring their effective use in

Table 1 Overview on guidance documents

Items	Acronym					
	GEP	GPP	ISPOR	EnCePP	AHRQ	STROBE
Title	Good epidemiological practice	Good pharmacoepidemiology practices	Good practices for real-world data studies of treatment and/or comparative effectiveness	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance	Agency for Healthcare Research and Quality	STrengthening the Reporting of OBservational studies in Epidemiology
Issued by	Deutsche Gesellschaft für Epidemiologie	ISPE	ISPOR and ISPE	EMA	U.S. Department of Health and Human Services	STROBE initiative
Years (first > current)	1999>2019	1996>2016	2017	2011>2023	2007>2020	2007> ongoing
Number of pages	17	9	7	141	426	6+32
Focus on	Ethics, research question, protocol, data protection, quality assurance, data storage, interpretation, publication, communication	Additional aspects rarely covered by guidelines: set-up, conduct, analysis, archiving	Differentiation between HETE versus exploratory study; registration of protocol; replication of results; external validation; authorship; inclusion of key stakeholders	All aspects. Guideline refers to all other documents in this table	All aspects	Optimized reporting and implicitly planning of such studies. The main analytical designs: cohort, case-control, and cross-sectional studies. No guidance on ethics, ownership, authorship
Reference	(34)	(35)	(36)	(37)	(38)	(39)

EMA, European Medicines Agency; HETE, Hypothesis Evaluation Treatment Effectiveness; ISPE, International Society of Pharmacoepidemiology; ISPOR, International Society for Pharmacoeconomics and Outcomes Research.

HTA. It is particularly valuable for evidence developers who aim to demonstrate the robustness of their registries and for international organizations that rely on registry data for HTA and regulatory decision-making (47). By setting clear quality benchmarks, tools like REQueST facilitate the optimal use of registry data across a variety of contexts, ensuring that decisions based on such data are well-founded and credible.

EHRs as potential replacements for registries

EHRs have emerged as transformative tools in healthcare, with the potential to complement or even replace traditional registries. By offering a centralized data repository that integrates patient data across multiple institutions and over extended periods, EHRs provide a unique opportunity for large-scale data collection and analysis.

One of the most significant advantages of EHRs is their ability to capture real-time data. Unlike traditional registries, which often rely on periodic data entry, EHRs record patient information as part of routine clinical care. This reduces the lag between data collection and analysis, enabling more timely insights into patient outcomes and trends.

Another key strength of EHRs lies in their scalability. EHRs can aggregate vast amounts of data from diverse patient populations, covering a wide range of demographics, conditions, and treatments. This breadth allows for the creation of large-scale datasets that are invaluable for conducting comparative effectiveness studies, identifying treatment patterns, and analyzing long-term outcomes. For example, a study conducted across the University of

Table 2 Quality checklists and assessment tools

Society/institution	Acronym	Country	Year	Guidance document	Reference
National Institute for Health and Care Excellence	NICE	UK	2012	Appendix H: appraisal checklists, evidence tables, GRADE and economic profiles	(43)
				NICE real-world evidence framework. Conduct of quantitative real-world evidence studies	(44)
National Institutes of Health	NIH	USA	2013	Study Quality Assessment Tools	(45)
Institute for Quality and Efficiency in Health Care	IQWiG	Germany	2020	Concepts for the generation of routine practice data and their analysis for the benefit assessment of drugs according to §35a Social Code Book V (SGB V)1 Appendix C—Quality criteria for registries and registry studies in the literature	(46)
Agency for Healthcare Research and Quality	AHRQ	USA	2020	Registries for Evaluating Patient Outcomes: A User's Guide (Internet). 4th edition. Chapter 14 Assessing Quality	(38)
European Network für Health Technology Assessment	EUnetHTA	Europe	2020	The REQueST	(47)
European Medicines Agency	EMA	European Union	2021	Guideline on registry-based studies	(32)

REQueST, Registry Evaluation and Quality Standards Tool.

California Health system demonstrated the utility of EHRs in evaluating the safety and effectiveness of various therapies for type 2 diabetes (48).

EHRs also facilitate the integration of multiple data types, including laboratory results, imaging data, and physician notes, providing a holistic view of patient care. This richness of information enables researchers to perform nuanced analyses and gain deeper insights into the complexities of healthcare delivery and outcomes. Moreover, advanced analytical tools, such as artificial intelligence and machine learning, can be applied to EHR data to uncover patterns and predict trends that would be difficult to discern using traditional registries.

Cost efficiency is another compelling advantage. While setting up and maintaining traditional registries can be resource-intensive, leveraging existing EHR systems minimizes the need for separate infrastructure. This efficiency not only reduces costs but also eliminates duplication of effort, making data collection more streamlined and sustainable.

However, EHRs are not without challenges. One of the primary concerns is data quality. EHRs are designed for clinical care rather than research, which can lead to variability in data completeness and accuracy. Missing or inconsistent data can compromise the validity of research findings, necessitating robust data validation and cleaning processes.

Data privacy and security are also critical issues. The use of EHRs for research requires strict compliance with regulations such as the General Data Protection Regulation (GDPR) in Europe or the Health Insurance Portability and Accountability Act (HIPAA) in the USA. Ensuring patient consent and maintaining confidentiality are essential to addressing ethical and legal concerns.

Another limitation is the potential for bias in EHR data. Patients included in EHR systems may not be representative of the broader population, particularly if access to healthcare is uneven. Additionally, confounding variables inherent in observational data must be accounted for through methods such as propensity score matching to ensure robust and reliable results (49).

Interoperability is another significant hurdle. EHR systems often use proprietary formats and standards, making it challenging to integrate data across different platforms. Efforts to standardize data formats, such as the adoption of Fast Healthcare Interoperability Resources (FHIR), are critical to unlocking the full potential of EHRs as registry replacements (50).

Despite these challenges, the potential of EHRs to revolutionize data collection and analysis in healthcare is undeniable. With advancements in data standardization, interoperability, and analytical tools, many of the current limitations of EHRs can be mitigated. Furthermore, initiatives to enhance data quality and ensure compliance with regulatory standards are paving the way for more reliable and ethical use of EHRs in research.

By addressing current limitations through technological and regulatory advancements, EHRs have the potential to transform the landscape of clinical research.

Conclusions

Setting up an international registry, in cardiology, congenital cardiology or congenital heart surgery and other fields, requires careful consideration of scientific, regulatory, and methodological aspects. By adhering to established guidelines and quality indicators, registries can provide reliable and reliable RWD, enhancing clinical research and healthcare outcomes. The integration of EHRs presents a promising avenue for future registries, enabling large-scale, continuous data collection and analysis.

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