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REVIEW

Real world evidence: Perspectives from a European Society of Cardiology Cardiovascular Round Table with contribution from the European Medicines Agency

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Real world data (RWD) refers to healthcare information that is routinely collected in electronic healthcare records (EHR), hospital and pharmacy records, patient and disease registries, and health insurance databases. The collection and analysis of this vast amount of data is an important complement to that obtained from conventional randomised controlled trials (RCT). Real world data has been used for healthcare quality improvements, to conduct clinical trials, to support drug and device development, and to inform medical guidelines. The utility of RWD may be facilitated by common data models, which standardise format and content, and allow data from different health systems to be analysed together.

The European Society of Cardiology (ESC) supports the use of RWD in collaboration with national cardiac societies, regulatory authorities, and industry to encourage continuous quality of care improvements at the hospital and country level, to conduct registry-based randomised clinical trials (R-RCT) and to facilitate safety surveillance of novel drugs and devices.

The European Medicines Agency (EMA) is developing systems and processes to enable the use of RWD that can help in trial planning, defining clinical contexts, and enhancing outcome assessments. RWD can also contribute to the measurement of the impact of regulatory actions, such as contraindications or restriction of indications by looking at medicines use patterns over time across European Member States. A number of other initiatives from the European Commission and the EMA are underway to strengthen the EU's health security framework, and foster the collection and utilisation of RWD.

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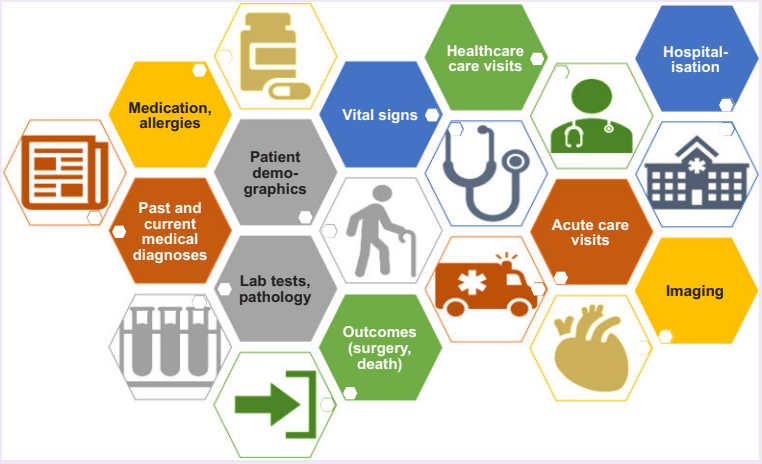
Graphical Abstract

Examples of types of data that can be collected as part of routine care.



Keywords DARWIN EU • Electronic healthcare records • EuroHeart • Fit-for-purpose registries • Registry-based randomised clinical trials

Introduction

The rapid evolution of technology has made it possible to collect large amounts of routine healthcare data. A key advance in data collection has been the development of common data models (CDM) to standardise format and content, such as common terminologies, vocabularies, and coding schemes to help facilitate interoperability and data pooling across various RWD sources. Some CDMs include the Sentinel System, the National Patient-Centered Clinical Research Network (PCORnet), and the Observational Medical Outcomes Partnership (OMOP) CDM.[1]

Information about patient health status or healthcare delivery that are routinely collected from a wide variety of sources, including electronic healthcare records (EHR), hospital and pharmacy records, patient and disease registries, and health insurance databases (claims data) are often referred to as real-world data (RWD).[2–6] Real word evidence (RWE) is often used to describe the evidence derived from the analysis of RWD, which can provide information about the use of treatments, risks, and prognosis, and it is used to support regulatory, reimbursement, and clinical decision making.[2–7]

Real world evidence can be used to improve quality of care and clinical outcomes by providing a more comprehensive understanding of the effectiveness and safety of cardiovascular therapies, as traditional clinical trials may not fully capture the range of patient populations or treatment scenarios that are seen in clinical practice. For example cohort studies linked exposure to angiotensin-converting enzyme inhibitors during the first trimester with an increased risk of congenital malformations in newborns, leading to additional safety measures.[8] Real world evidence played also a major role in the identification of increased cardiovascular risk with rofecoxib.[9] Analyses of large databases may capture safety signals when the incidence of adverse events is too low to be detected in randomized trials; for example, diabetic ketoacidosis among users of SGLT-2 inhibitors.[10] Apart from efficacy and safety assessments, RWE can be also used to assess the utilization of cardiovascular therapies, including adherence to treatment guidelines.[11]

This document was developed from discussions among experts during a Cardiovascular Round Table workshop supported by the European Society of Cardiology (ESC) with contributions from the European Medicines Agency (EMA). The report was developed through a collaborative effort that included perspectives from regulators, academia, and industry. It provides an overview of European initiatives to improve the use of RWD, and to describe the valuable role that it can play in terms of informing clinical practice, conducting clinical trials, supporting drug development, and informing regulatory decision-making.

Using real world data for healthcare quality improvements

Registries can provide valuable data for various purposes but all have limitations such as lack of standardisation, lack of representativeness, heterogeneous quality, or governance that limits data sharing. National registries such as SWEDEHEART, provide country-wide data with long-term follow-up, however, they cover a specific population and may not be generalisable to other localities. Based on experience from the EUROobservational Research Programme (EORP), and the success of national registries, the ESC determined that there was a need to improve the quality of observational data collected, and to expand registries to include continuous quality of care improvements, device monitoring, and registry-based randomised clinical trials (R-RCT).[12] In 2019, the ESC agreed to coordinate and sponsor the development of the European Unified Registries On Heart care Evaluation And Randomized Trials (EuroHeart, www.escardio.org/Research/euroheart). EuroHeart supports the development of national and regional registry programmes using common EuroHeart datasets for common cardiovascular diseases (CVD), with the infrastructure (hardware and software) and the data sets belonging to the individual countries. EuroHeart also provides an optional IT-infrastructure allowing continuous quality development at the hospital and country level and the performance of collaborative research such as R-RCTs, and safety surveillance of novel drugs and devices. The data allows comparisons of the quality of care within hospitals, across regions, or between different countries.

Using a structured process, the EuroHeart group have developed harmonised data standards for acute coronary syndrome (ACS) and percutaneous coronary intervention (PCI), heart failure (HF), atrial

Table 1 Potential benefits and challenges of R-RCTs[15,17–20]

Potential benefits	Potential challenges
• Potentially less expensive designs • Minimally-selected consecutive patient enrolment • Electronic informed consent • Faster patient enrolment • Facilitated collection of baseline variables, identification of eligible patients and potential trial sites • Simplified randomisation • Reduced clinician burden (embedded in routine care) • Registry and other databases can be used to collect outcome data—efficient follow-up, no need for trial-specific patient visits • Potential for more complete, and very long-term follow-up • Enhanced generalisability of results • Evaluation of eventual implementation of trial results	• Registry data quality, and consistency • Patient safety reporting • Lack of or incomplete outcome variables • Adjudicating patient-report outcome events may increase complexity • Ensuring the representativeness of participants (particularly broader geographic involvement) • Matching the database to the research questions • Transparency and workload for developing robust coding systems • Funding (multi-stakeholder support is needed)

fibrillation (AF), and valvular disease.[13,14] Using the EuroHeart IT-platform and these standardised, structured variables, provides data that can be used for on-line monitoring of processes of care and outcomes, monitoring of clinical trials on drugs and devices, and form a basis for observational research.

Using real world data to conduct clinical trials

Real world data can be used to facilitate the conduct of clinical trials, including providing data on the natural history of the disease, as well as helping with trial design, patient identification and recruitment.[15–17] Registries, claims data, and EHR data can be used to screen large numbers of patients and to identify trial sites, and thus speed up enrolment.[15,17,18] There is the potential to substantially reduce the time and cost of conducting trials.[15,17,18] While observational data cannot replace RCTs, RWD can complement RCTs by providing supportive safety and efficacy data on therapies for regulatory decision-making, and helping in the identification of clinical characteristics associated with trial outcomes.

The R-RCT is being increasingly used in cardiology. R-RCTs involve patient randomisation and data capture from within a registry, combining the features of a prospective RCT with a large-scale clinical registry.[15,17–20]

Although R-RCTs offer an efficient and cost-effective alternative to traditional RCTs, it is important to consider the challenges related to data quality, methodological shortcomings, and ethical issues, when conducting R-RCTs using registry data. The definition, collection, and accuracy of baseline data gathered in registries may vary. Additionally, outcome data documented in registries may be subject to uncertainty, and registries may have missing data or fail to capture important prognostic factors. Methodological issues include: ensuring the representativeness of study participants in recruitment from registries; limitations imposed by the registry characteristics to trial designs, and types of outcomes. Ethical issues include, among others, potential lack of consent of registry participants for screening their records for trial inclusion.

The significant variability within R-RCTs designs such as processes for ethics and consent, randomisation, data collection, outcome data, and trial reporting, limits their ability to replace conventional RCTs for regulatory purposes.[21] The latter remain the gold standard to determine efficacy of drugs and devices. Some of the potential benefits and challenges associated with R-RCTs are shown in *Table 1*.[15,17–20]

Thrombus Aspiration in ST-Elevation Myocardial Infarction in Scandinavia (TASTE) is an example of a R-RCT clinical trial that led to changes in clinical practice.[22,23] A previous RCT, Thrombus Aspiration during Percutaneous Coronary Intervention in Acute Myocardial Infarction Study (TAPAS; $n = 1071$), suggested a 50% lower mortality rate with thrombus aspiration among patients with ST-segment elevation myocardial infarction (STEMI).[24,25] However, TAPAS was underpowered to demonstrate effects on mortality, which was a secondary endpoint. Subsequently, the TASTE trial—an open-label, RCT that used a population-based registry to expedite patient enrolment and data collection was conducted.[22,23] Over 7000 patients were randomised and no benefits were found on mortality associated with routine thrombus aspiration at 1-year follow-up.[23]

This data led to changes in guidelines[26,27] and in clinical practice.[28] In 2012 ESC guidelines recommended considering routine thrombus aspiration (Grade IIa),[26] however, in the 2017 update a recommendation against this practice (class III) was included,[27] based on the TASTE trial[22,23] and the Trial of Routine Aspiration Thrombectomy with PCI versus PCI Alone in Patients with STEMI (TOTAL) trial.[29,30]

The use of registries to conduct trials is increasing rapidly. For example, in cardiology there are more than a dozen R-RCTs currently ongoing in Sweden (www.ucr.uu.se/swedeheart/), with many more studies already completed and published.[31] It is hoped that EuroHeart will provide an opportunity to conduct R-RCTs on treatment strategies, procedures, medical devices, and pharmaceutical agents.

Electronic healthcare records systems now provide an alternative approach to conduct RCTs, based in either community or hospital environments. DaRe2THINK (healthcare Data for pragmatic clinical Research in the NHS—primary 2 secondary) is an England-wide healthcare-embedded clinical trial in primary care with linkage to the totality of secondary care records.[17] The platform reduces burden on clinical staff and patients, with an entirely 'no-visit' approach, including remote e-consent and follow-up. The first trial, initiated in July 2021 (https://clinicaltrials.gov/ct2/show/NCT04700826) is investigating whether starting direct oral anticoagulants earlier in patients with atrial fibrillation can prevent adverse clinical events and cognitive decline during 5- and 10-year follow-up. A range of other digital innovations are now being increasingly used around the world to aid in recruitment, retention, and follow-up of patients enrolled in clinical trials.[32] As with registry-based trials, EHR trials have their own set of limitations (including the underlying coding), thus successful deployment of these innovations is dependent on the intervention and clinical scenario.

Using real world data to support drug development

Industry development of fit-for-purpose real word evidence databases

When developing registries, industry follows best practice guidelines for RWE frameworks such as those from the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA).[4,33] Ideally, registries are designed using federated data and database networks, validated algorithms, and standard statistical methods. Generally, the registries are 'fit-for-purpose', meaning they are designed to provide data to address a specific research question.

An example of a large industry-led RWD programs is ACROPOLIS™ (Apixaban ExperienCe Through Real-WOrld POpuLatIon Studies). This global program is assessing the effectiveness and safety of anticoagulants using RWD among patients with non-valvular atrial fibrillation (NVAF) and venous thromboembolism (VTE). The program provides confirmation of RCT data, expanded data on sub-populations not well represented in RCTs, and more widely geographically distributed data. ACROPOLIS has taken a step-wise approach since its launch in 2015, progressively adding disease states, outcomes, comparator groups, and subpopulations. Data are being collected in many countries around the globe, through studies such as ARISTOPHANES (Anticoagulants for Reduction in Stroke: Observational Pooled Analysis on Health Outcomes and Experience of Patients) in the US, NAXOS (Evaluation of Apixaban in Stroke and Systemic Embolism Prevention in Patients With Nonvalvular Atrial Fibrillation) in France,[34] and BEYOND (Benefit of NOACs study of non-valvular AF patients in Nordic countries) in Norway, Denmark, and Sweden.[35] Results of RWD studies in the ACROPOLIS program are highly consistent with RCTs, including the ARISTOTLE (Apixaban for Reduction In Stroke and other ThrOmboembolic Events in Atrial Fibrillation) trial for stroke prevention,[36–42] as well as with the AMPLIFY (Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy) trial in VTE treatment.[43] The ACROPOLIS program has generated relevant and high quality data that has been referenced in many guidelines.[44–49]

Role of industry-driven registries

With the increasing number of registries being developed by professional societies and regulatory authorities, there is continuing discussions over whether or not industry needs to develop proprietary registries. These discussions should integrate guidance from the EMA, which states that from a regulatory perspective, product specific registries are to be considered non-interventional post-authorisation studies and existing disease registries should preferably be used to collect comprehensive data on various treatments.[33] While there is a need to avoid duplication of efforts, industry researchers can play an important role in designing and implementing effective disease registry networks. They can provide expertise in study design and analysis, in-house data from multiple geographies, and have extensive existing external academic and commercial research collaborations. They can also provide operational and financial support.

Whenever possible it would be preferable for industry to collaborate with other groups to conduct long-term fit-for-purpose registries that can be used across disease specialities. However, use of existing disease registries requires mechanisms to be in place to allow industry to obtain additional data and perform additional analyses. To avoid duplication of efforts industry should support the development and maintenance of fit-for-purpose disease registries to meet the needs of multiple stakeholders, particularly for rare diseases.

Using electronic healthcare records to collect real world data

Electronic healthcare records systems are becoming increasingly widespread and standardised, and beginning to be used for research to help answer clinical questions. For example, a study using EHR data from the Valencia Community, looked at the impact of adherence to guidelines for secondary prevention in the real world. The study included 92 436 patients who had experienced a major CV event (MACE), and found that the use of increasing numbers of drugs for secondary prevention was associated with reductions in mortality over at least 1-year of follow-up.[50] Another example is LEGEND-HTN (Large-Scale Evidence Generation and Evaluation in a Network of Databases- hypertension) using multiple global RWD sources to accrue data on hypertension treatment for 4.9 million patients.[51]

In the UK, the National Health Service (NHS) Digital's Trusted Research Environment (TRE) makes large-scale research possible (www.digital.nhs.uk). The TRE is a government supported, UK-wide resource connecting primary and secondary care with national coded databases and registries, with linked person-level anonymised data that is updated regularly.[52,53] Patient consent is not required, but there is an national opt-out process. Lifelong patient data are collected for almost 60 million patients. More granular data are available from the Health Data Research UK (HDR-UK) hubs. PIONEER, the HRD-UK Hub for acute care (www.pioneerdatahub.co.uk) has 20 years of longitudinal data including over 1.2 million patient records from ambulance services and over 150 hospitals.[54,55] Detailed data on patient observations, imaging, and outcomes can now be collected throughout the patient journey (Graphical abstract).[55]

With the advent of such large datasets, new analytical pipelines have become increasingly vital. A broad array of 'artificial intelligence' (AI) algorithms has been developed to use machine-learning approaches that can account for multi-morbidity, discover therapeutic targets, and provide data-driven hypothesis testing.[56–58] This remains an evolving field, with clear frameworks needed to ensure transparency, iterative improvement and validation prior to implementation into clinical practice.

Using real world data to support regulatory decisions

Real world data can be used to support regulatory processes in a number of different ways, including facilitating trial planning, defining the clinical context, and assessing treatment outcomes (*Table 2*). Real world data can also be used to assess the impact of regulatory actions, such as the effects of contraindications or restriction of indications of medicines on prescribing practices.

Table 3 shows studies looking at the use of RWE in applications for marketing approvals, in both the Europe and the US.[7,59,60] In these studies, the use of RWE was highly variable due to different definitions, types of included submissions, and methodologies/study periods. The most common RWD sources were registries and hospital data, and RWE was mainly used to support safety, and less often to support efficacy.[7,60] In an analysis of 136 FDA approvals, RWE influenced regulatory decisions in almost 75% of the applications where it was provided.[60] In a similar analysis of EMA approvals, RWD around efficacy/effectiveness claims in pre-authorisation packages was found to support regulatory decisions in 5 of 16 (31%) marketing authorisation applications (MAAs) and 5 of 10 (50%) extension of indication applications (EoIs), but did not support decisions in 11 cases (7 MAAs, 4 EoIs).[61] Common limitations included missing data, population not representative, small sample size, inadequate analysis plan, and risk of bias. However, it is difficult to assess the true impact

Table 2 Areas where RWD can support regulatory decision making

Support trial planning & study validity	Help define the clinical context	Explore associations and impact
• Planning phase o Study design o Feasibility • Completed studies o Representativeness o Validity	• Epidemiology of disease • Natural course of illness • Clinical standards of care • Drug utilisation	• Effectiveness • Safety • Impact of regulatory decisions

Adapted from reference.[63]

Table 3 Use of real-world evidence in marketing authorisation applications for medicines

	Flynn *et al.* 2022, EMA[7]	Eskola *et al.* 2022, EMA[59]	Purpura *et al.* 2022, FDA[60]
Number of products	158	111	136
Period	Jan 2018–Dec 2019	Jan 2018–Dec 2019	Jan 2019–June 2021
Products with RWE included	63 (39.9%)	111 (100%)	116 (85.2%)
Therapeutic areas with more use of RWE	Oncology and anti-infectives	Oncology, haematology and anti-infectives	Oncology and anti-infectives

of RWE, as it needs to be considered in the context of the full data package.

To help strengthen the use of RWD in regulatory decisions, a Europe-wide initiative has been developed. In Feb 2022, the EMA and the Heads of Medicines Agencies (HMA) launched the Data Analysis and Real World Interrogation Network (DARWIN EU®).[62] The Erasmus University Medical Centre Rotterdam is acting as the coordination centre. The EU Regulatory Network will be the principal user of DARWIN EU® to support its decision-making on medicines. DARWIN EU® is a federated network of data using the OMOP CDM and the data stays local. The data will be used to perform studies in a timely manner and increase consistency of results. The system will include routinely collected health data from different settings (primary and secondary care) and populations, and from different sources (e.g. EHRs and claims databases). Over 3000 automated data checks are performed to ensure the quality and completeness of the data. The goals and function of the program are shown in *Figure 1*.[63]

Types of analyses and studies that will be possible with DARWIN EU® include assessments of drug utilisation, safety monitoring, health outcomes, and population characteristics.[63] More complex studies will also be conducted such as measuring the association between a drug exposure and health outcomes that considers potential confounding factors. DARWIN EU® is currently in the establishment and pilot mode, and a dedicated publicly-available website is expected to launch in 2023, in addition to the information available on the EMA website.[62]

In parallel, industry is developing study frameworks for generating multi-country epidemiological evidence based on the DARWIN EU® principles: implementing CDMs, leveraging both external and in-house data sources from multiple geographies, and collaborating with both commercial and academic partners for data access and analysis.[64] Such studies will further benefit from broader utilisation of OMOP and can rapidly generate global data on disease burden, treatment patterns, and clinical outcomes. However, even using a CDM, attention must be paid to interpreting data from different data sources, coding systems, and healthcare environments.

Challenges and opportunities in using real world data for regulatory decisions

There are challenges associated with using RWD to generate RWE, including potential operational, technical, and methodological difficulties.[5] The use of RWE studies for regulatory approval is associated with several well-known limitations such as: potential of not including consecutive patients, and risks of bias and confounding, which may result from limited control over treatment decisions in real world settings. It is difficult to draw causal inferences about the effectiveness and safety of medical technologies assessed outside of RCT settings in the absence of appropriately defined control groups. In addition, since RWE is often generated from EHRs or claims databases, there is the potential for incomplete or inaccurate information.

From the operational perspective, RWD sources governance, and sustainability issues can complicate access to data. In addition, technical aspects such as lack of consistent standardised terminology, case definitions, and data format, may impair data quality (e.g. completeness and accuracy) and linkage/interoperability. Methodologically, it can be difficult to determine the validity and reliability of data that may have been collected for purposes other than research.

Some of the strategies to overcome the challenges include early and repeated consideration and dialogue among all relevant stakeholders on the need for RWD during drug development. There is a need for regulatory guidance for characterisation of sources, and the publication of characteristics, governance, and processes for sharing of the data sources to enable discovery of suitable data to answer a specific research question. The usability of RWD would be enhanced by internationally agreed data formats and terminologies including CDMs or protocols.[5] This is not an exhaustive list of enablers. Methodological standards such as the European Network for Centres of Pharmacoepidemiology and Pharmacovigilance (ENCePP) ensure good practices around the use of RWD and provide guidance on quality assurance and control procedures.[65] Long-term funding is critical to guarantee sustainability of the RWD sources, to maintain the database systems, and to ensure ongoing high quality management processes and staff training.

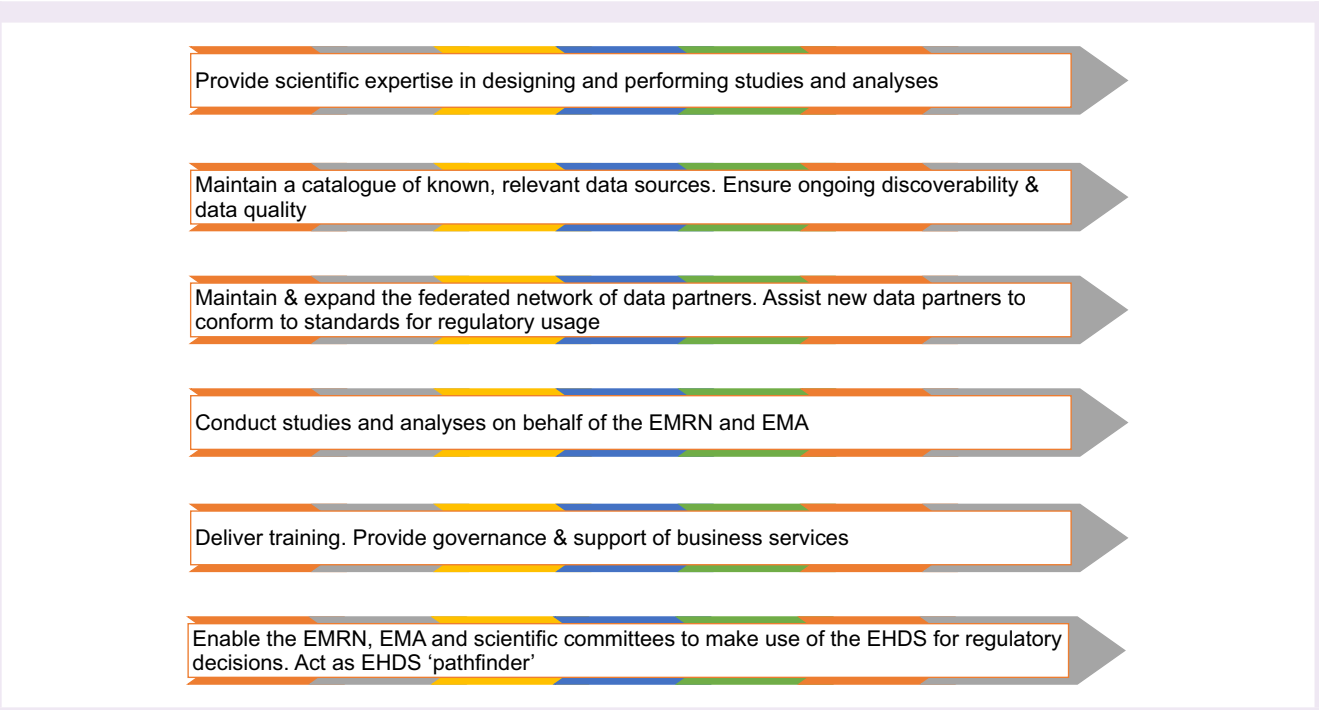


Figure 1 Goals and function of DARWIN EU®. Adapted from reference.[63] EHDS, European Health Data Space; EMA, European Medicines Agency/EMRN, European Medicines Regulatory Network.

Table 4 EU Health agenda: Main initiatives relevant to real world evidence collection and use

- European Health Union package
- Health Technology Assessment regulation
- Implementation of the clinical trials framework
- Implementation of Medical Devices Regulation
- Proposal for a European Health Data Space (EHDS)
- Revision of the blood tissue cells (BTC) legislation
- Revision of the basic pharmaceutical acts: Directive 2001/83/EC & Regulation (EC) No 726/2004
- Revision of the orphan and paediatric legislation

Refer to the European Commission website for more information on these and other initiatives (https://ec.europa.eu/).

Table 5 Opportunities to enable the use of high quality RWD in decision making

- DARWIN EU®
- Data quality & representativeness
- Data discoverability
- EU Network skills
- EU Network processes
- Network capability to analyse
- Delivery of expert advice
- Governance framework
- International initiatives
- EU BD stakeholder implementation forum
- Veterinary recommendations

Adapted from reference.[67,68]

Initiatives to improve the quality of real world data

Regulatory bodies are increasingly recognising the importance of RWD. The European Commission has a number of initiatives underway to strengthen the EU's health security framework and medicines regulation, and facilitate the collection and use of RWD (https://ec.europa.eu/) (*Table 4*).

One important initiative from the European Commission is the European Health Data Space (EHDS).[66] The EHDS will provide rules, common standards, infrastructures, and a governance framework for the use of data from EHR systems for healthcare, research, innovation, and policy making. The MyHealth@EU platform is designed to empower individuals to access and control their personal health data, and it ensure a consistent framework for use of health data for research, and other purposes.

In addition, the HMA-EMA joint Big Data Steering Group (BDSG) has issued 11 recommendations for areas to focus on (*Table 5*) to enable the use of high quality RWD in regulatory decision making of human (and veterinary) medicinal products.[67,68]

Some of the key initiatives stem from a collaboration with the joint action 'Towards A European Health Data Space—TEHDAS' focused on establishing an EU framework for data quality and representativeness, and an EMA data source catalogue to improve data discoverability (expected in mid- to late-2023). A Methodological Working Party with scientific leadership from across the EU Network is working on developing a roadmap for comprehensive guidance across data and methods in epidemiology and statistics.[67]

Transparency is essential when using routinely-collected healthcare data, either from registries or via EHRs. For this reason, the BigData@Heart consortium and ESC, with international multistakeholder input have developed CODE-EHR, a best practice

Table 6 Practical questions and answers around the use of RWD

- Registries are providing retrospective data, with a time lag potentially of years, will newer systems improve this?
  - Particularly because of COVID-19, the time to get data has shortened. In DARWIN EU® increasing numbers of partnership are being developed with data sources across Europe. The use of the CDM has made updates automated, with some date being updated monthly or weekly
  - Increasing use of artificial intelligence to analyse data will also speed access
- What is required for successful implementation of registries?
  - Among the key requirements for success are infrastructure and funding sources. Ongoing investment is needed from cardiac societies, industry, and government bodies
  - There is a need for international collaboration, which can be facilitated by leadership from the ESC and other societies
- When using RWD, how can we bridge the divide between the need for technical expertise and the clinical reality of everyday patient care?
  - The field of health informatics has been developing along with the EHR technology.
  - SNOMED CT (Systematized Nomenclature of Medicine—Clinical Terms) provides a clinical terminology code that helps to define what coded information means for clinicians
  - CDMs such as OMOP are being used extensively in Europe, and there are groups of bioinformaticians and machine learning specialists, working with clinicians at every level to help hospitals make the transition to these systems
  - The EuroHeart collaboration is developing structured data standards on key patient characteristics, processes of care, outcomes, and quality indicators in major CVDs. Data are amenable to online statistical analyses supporting continuous improvement of care and providing continuous CRFs for research projects
- How can we ensure EHRs or registries are collecting all the clinical information that is needed (e.g. comorbidities), and that data are accurate for use in trials?
  - There is the ability to customise EHRs to include additional data, and these systems are increasingly moving toward greater standardisation
  - Electronic transfer of data from registries into her and frherEHR into registries is already occurring and likely to increase in the future, which help ensure more complete information
  - One of the key factors is to choose the correct data source for the question the trial is trying to answer
- How can we ensure that healthcare staff have the capacity to collect and record all of this data across health systems?
  - Use of EHR will not require duplication of efforts, such as those that are currently needed for most clinical trials and registries
  - Integration of EHR and registries should also help reduce redundant work
- How can we ensure that registries or data collection systems are designed and managed so that they are multi-purpose?
  - Collaboration between industry, professional societies, and regulatory authorities is extremely important. Registries or data systems must be multi-purpose, keeping in mind that the goal of all stakeholders is to improve patient care
  - Existing registry data that has been collected by industry for approval purposes should be reanalysed to put the patient at the centre; looking at safety, appropriate use, and the value brought to the patient rather than answering questions just for regulatory or reimbursement purposes
- How can we ensure true consecutive patient enrolment with RWD, unless the registry is mandated by government legislation?
  - EuroHeart will show whether this is possible on an international level based on the SWEDEHEART experience. EuroHeart is primarily designed for quality improvement purposes. Data should be collected on consecutive patients, if it is not, this will be reported as a quality indicator in itself
  - The use of patient associations are pivotal to increase inclusion of all patients with a specific disease. Increasing the involvement of patients will benefit statistical analyses and registries
- Can registries look at physician uptake of guidelines and long-term patient adherence/persistence with GDMT?
  - In EUROHEART adherence to GDMT is collected as a quality indicator, when data on patient's discharge medication are collected. The data shows the proportion of patients with an indication and without a contraindication that were treated with GDMT each week. Currently, long-term follow-up out of hospital is an issue, but data show that 80% of patients will be on the drugs they were discharged on at one-year follow-up
  - DARWIN EU® can conduct drug utilisation and treatment duration studies, and repeat these over time
- Will data protection legislation hinder the use of DARWIN EU®, EuroHeart, the EHDS, and other registries or EHR systems across countries?
  - The EHDS is not yet operational, but should allow data sharing across countries
  - Systems such as DARWIN EU® are using a federated model where the data are not passed on from the data holder to the coordination centre, but rather analysed locally. Only the results which are anonymised and aggregated are shared onwards. That reduces the requirements for any data protection considerations
  - Similarly, data collected for quality improvement purposes, such as in EuroHeart, does not require patient informed consent

CRF, Case report form; CDM, common data model; EHR, electronic health record; EHDS, European health data space; GDMT, guideline-directed medical therapy; OMOP, Observational Medical Outcomes Partnership; RWD, real-world data.

framework for the use of structured healthcare data in clinical research.[69–71] A social license and mandate for research using these data sources is paramount for long-term sustainability, thus, involving patients and the public in both research design and management is a critical step. Extensive patient involvement will also help to ensure the development of systems focused on the needs and wants of patients.

Practical questions and answers

This ESC CRT meeting provided a detailed overview of the ongoing efforts to increase the quantity and strengthen the quality of RWD for use in research and regulatory decisions, and to ultimately guide and improve clinical care for cardiology patients. Throughout the meeting some of the main concerns of clinicians and researchers around the use of RWD were discussed. *Table 6* summarises some of these issues.

Further steps and opportunities

There are a number of ESC Data Collection initiatives underway including the Data Science Centre, a relaunch of the registries department, and the consolidation phase of EuroHeart. In addition, there is a need for greater support for the development of a secure

European Union technology ecosystem/infrastructure to increase the capacity for Member States to share and exchange information on CVDs, as well as continued work on the development of common datasets. Finally, support for the development of the planned EHDS will facilitate the use of health data for the provision of healthcare and research.

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All CRT members that were included as authors contributed to design of the CRT meeting and to selection of the topics; P.S. and S.J. drafted the initial manuscript. All authors critically revised the manuscript, gave final approval, and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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No new data were generated or analysed in support of this research.

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