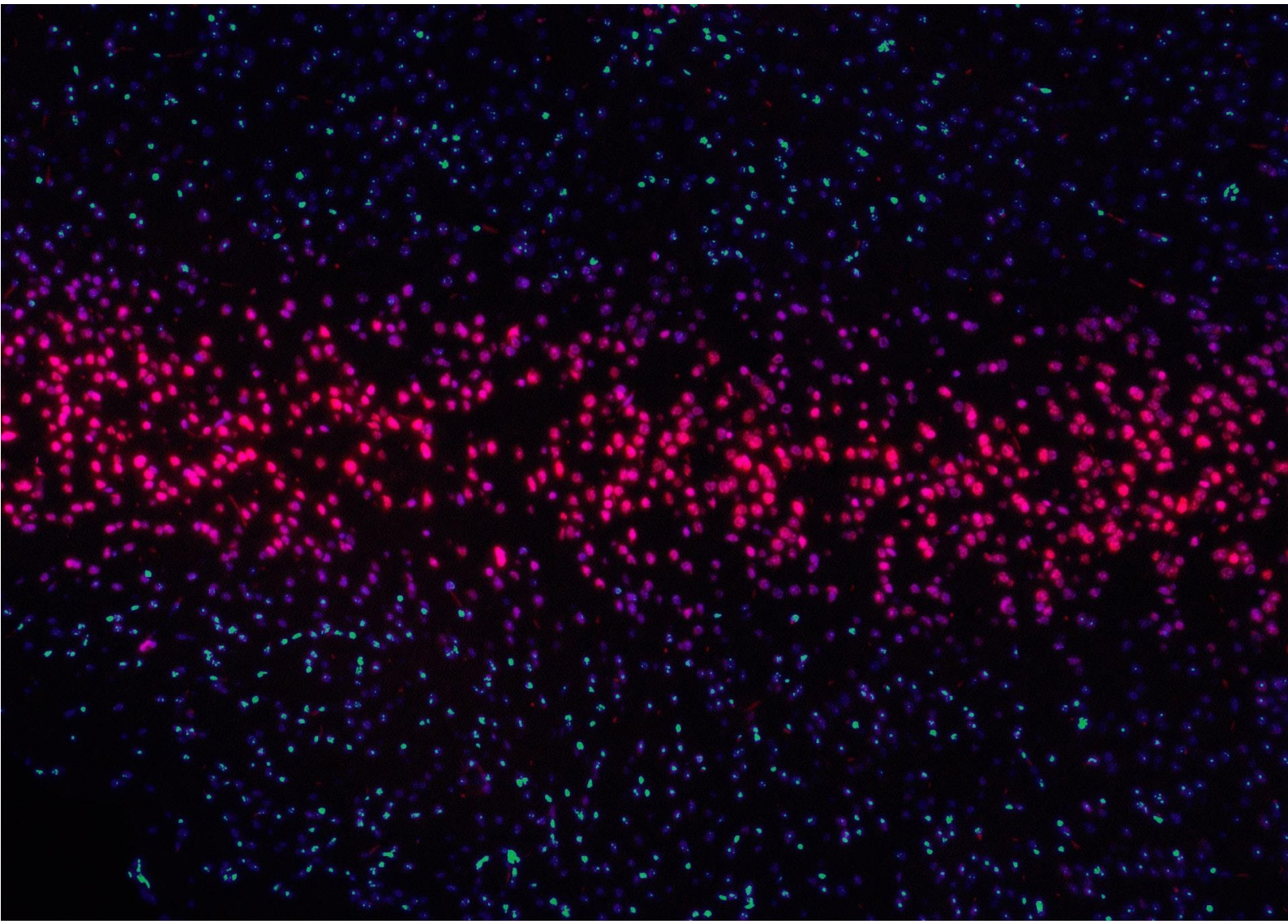
InteropEHRate
EHR in people's hands across Europe

Real-world evidence in health and care research: The contribution of InteropEHRate



White Paper

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InteropeEHRate is a research and innovation project funded by the Horizon 2020 programme that focuses on developing open specifications to allow citizen-centred data sharing. It is due to complete its work by September 2022.

Cover photo by National Cancer Institute

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List of abbreviations

API	Application Programming Interface
BYOD	Bring your own device
COVID-19	Coronavirus disease 2019
CRO	Clinical Research Organisation
DCT	Decentralised model of Clinical Trial
DTx	Digital therapeutics
EC	European Commission
EHDEN	European Health Data and Evidence Network
EHR	Electronic Health Record
EMR	Electronic Medical Record
ePRO	Electronic Patient-reported Outcome
ESB	External Stakeholders' Board
FHIR	Fast Healthcare Interoperability Resources
INTERVAL	InteropEHRate Validation
IRS	InteropEHRate Research Services
IT	Information technology
MDD	Medical Devices Directive
MDR	Medical Devices Regulation
MHMD	MyHealthMyData
NHS	National Health Service
PRO	Patient-reported outcome
PROM	Patient-reported outcome measure
QR	Quick Response
RCT	Randomised controlled trial
RDD	Research Definition Documents
RDS	Research Data Sharing
RRC	Reference Research Centre
RWE	Real-World Evidence
S-EHR	Smart Electronic Health Record
USA	United States of America

Executive summary

The importance of real-world data in health and care is coming to the fore. InteropEHRate is keen to offer insights into the opportunities that real-world evidence can offer in the field of research in health and care.

This White Paper explores the background to real-world data challenges in health and care. It focuses on European contributions to international initiatives in this field. It also draws attention to the growing impetus of hybrid approaches to health and care data collection.

The InteropEHRate vision for collecting data for research is to enable citizens to share health data with research centres without a direct intermediary and directly from their own smartphone.

This White Paper presents the InteropEHRate research platform composed by the research data sharing protocol, InteropEHRate Research Services and a reference implementation, and how research institutions benefit from these solutions.

1. Background: Real-world evidence

Evidence-based medicine[1] is based on the triad of evidence, experience, and choices: evidence from research, experience of physicians, and the choices/priorities of patients.[2]

Research in medicine provides new knowledge and innovative health treatment and services.

A vast amount of data available in electronic medical records (EMRs) is now being digitalised. It offers new opportunities for research that use a precision medicine approach and validate treatment options based on routine data. (Routine data is data collected in parallel to traditional data sources from classic clinical studies, for example.)

Real-World Data include health administrative data, electronic medical record data, primary care surveillance data, and disease registries. They are collected through health information systems, mobile applications or sensors. They provide a valuable source for Real-World Evidence (RWE) for decision making and research purposes. They are not collected through conventional randomised controlled trials (RCTs).

A 2020 survey conducted by the DigitalHealthEurope project found that respondents had a consistent willingness to share data with health researchers under specific circumstances (when the data was collected for not-for-profit organisations, and the data was anonymised).[3] This willingness on the part of citizens to share and provide data is likely to support more effective research data sharing, including through real-world data and real-world evidence. Its implications are relevant when exploring the use that InteropEHRate makes of data.

An overview of the background to real-world data provided InteropEHRate with insights into trends that have developed over the past 15 years; the challenges indicated by international initiatives, such as EHDEN; and the opportunities offered by a decentralised model of clinical trials.

1.1 Collecting real-world data: international trends

Open Science and Open Data have emerged as powerful trends in research policy and are supported by European Commission (EC) initiatives and policies. Open Science is an approach to the scientific process that focuses on spreading knowledge as soon as it is available using digital and collaborative technology and Open Data. Statistics and case studies related to accessing and reusing the data produced in the course of scientific production are available from the Open Science website of the EC.[4]

Yet, despite these trends, health data often remains locked in data silos that hamper its potential use in health innovation and research. In Europe, the organisation of research data

[1] Evidence-Based Medicine Working Group. "Evidence-based medicine. A new approach to teaching the practice of medicine". JAMA. 268 (17): 2420–25. November 1992

[2] The fields of health and care refer chiefly to patients; however, current policy directions in Europe focus on the role of the citizen. InteropEHRate uses both terms and considers the two terms as largely mutually replaceable.

[3] DigitalHealthEurope. Citizen-controlled health data sharing governance. October 2020. https://digitalhealtheurope.eu/wp-content/uploads/2020/11/Consultation-Paper-Citizen-controlled-health-data-sharing-governance.pdf

[4] https://ec.europa.eu/info/research-and-innovation/strategy/goals-research-and-innovation-policy/open-science/open-science-monitor/facts-and-figures-open-research-data_en

sharing reflects the fundamentally public and centralised nature of national and regional healthcare systems and infrastructures. **These centralised databases are difficult to access for research purposes. The three chief obstacles to doing this are organisational, legal, and technical.**

Over the last 15 or so years, a number of movements and initiatives have pledged their commitment to encouraging a larger role for citizens, as legitimate owners of their own data, in being able to share their data with research institutions.[5,6] Five examples follow – they range from European projects and their outcomes, national legislative and regulatory changes, to international initiatives:

- **MyHealthMyData** (MHMD)[7] is a Horizon 2020 Research and Innovation Action, which aims at changing the way sensitive data is shared. MHMD is poised to be the first open biomedical information network centred on the connection between organisations and individuals, encouraging hospitals to start making anonymised data available for open research while prompting citizens to become the ultimate 'owners' and controllers of their health data. MHMD is intended to become a real information marketplace, based on new mechanisms of trust and direct, value-based relationships among European citizens, hospitals, research centres, and businesses.
- **Salus.Coop**[8] is a data cooperative in Catalonia, Spain, that provides a platform for individual users to store and control their own health data. Through this platform, Salus.Coop aims to facilitate secure sharing of health data that enables citizens to control their own health records while incentivising data sharing to accelerate health research innovation.
- **Finland** has moved in new legislative directions and has set up a regulatory authority. The Finnish Parliament has approved an Act on the Secondary Use of Health and Social Data that entered into force on 1 May 2019.[9] This 2019 act widens the use of social and health data from research and statistics to sectors such as management, development, innovation, and education. FINDATA[10] is the Health and Social Data Permit Authority, that serves as a one-stop shop for the secondary use of health and social data.
- On an international level, there are various examples of data collection in the health and care fields. One initiative is **DataCollaboratives.org** from the United States of America (USA), a resource about creating public value by exchanging data, which outlines some relevant use cases (including health-related).

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[5] https://www.record-statement.org/

[6] Real-World Data for Coverage and Payment Decisions: The ISPOR Real-World Data Task Force Report. Value in Health. Volume 10, Number 5, 2007

[7] http://www.myhealthmydata.eu/

[8] http://saluscoop.org

[9] Finnish Ministry of Social Affairs and Health. Act on the Secondary Use of Health and Social Data. 26 April 2019 https://stm.fi/documents/1271139/1365571/The+Act+on+the+Secondary+Use+of+Health+and+Social+Data/a2bca08c-d067-3e54-45d1-18096de0ed76/The+Act+on+the+Secondary+Use+of+Health+and+Social+Data.pdf.

[10] https://www.findata.fi/en/

- Another international example is the **European Health Data & Evidence Network** (EHDEN)[11] which is part of the Innovative Medicines Initiative (IMI).[12] It aims to address challenges in generating insights and evidence from real-world clinical data at scale.

In Europe, however, addressing the solutions offered to challenges identified by EHDEN are not enough to unlock Real-World Data research perspectives. It is probable that other options are needed.

Similar obstacles to those identified by EHDEN are being experienced by other initiatives. The standard methodology underlying clinical research, based on clinical trials in order to develop new medicines, is facing similar dilemmas. In clinical trials, two of the most challenging difficulties are the recruitment of patient volunteers, and the avoidance of volunteer drop-out. The USA-based 2017-global Center for Information & Study on Clinical Research Participation survey reported that there were two main barriers to patients' participation: "lack of patients' awareness of clinical trials" (~61%); and the "geography and the distance to the clinical site" (60%)[13]. Another factor leading to patient drop-out from clinical trials is the burden on patients of participating in a trial, including the duration and number of clinical visits needed.

A decentralised model of clinical trials comes into play here as a more effective approach, since it can offer easier collection of real-world health data.

1.2 A decentralised model of clinical trials

The Decentralised model of Clinical Trials (DCTs) combines the adoption of remote application of selection criteria in studies based on medical records, follow-up based on digital endpoints, and telemedicine applied to clinical trials. **DCTs can improve patient access to trials, increase the participation of more diverse populations in those trials, and enhance data collection.**

Today, hybrid models to data collection are in operation. They combine DCTs with a traditional clinical trial approach, based on the specific needs of the disease or therapeutic area and study design.

Hybrid models are already used by the pharmaceutical industry and the clinical research community in Europe.

[11] https://www.ehden.eu/

[12] https://www.imi.europa

[13] Center for Information & Study on Clinical Research Participation (CISCRP). Perceptions & Insights Study. 2017

2. Enabling data collection: InteropEHRate's focus

Data collection in health and care has tremendous importance for furthering useful research. This section of the White Paper describes five general areas of data collection of principal interest to InteropEHRate.

The results of InteropEHRate are applicable to several health and care fields that can enable better data collection. The five areas under consideration include digital therapeutics, rare diseases and orphan drugs, patient-reported outcomes, COVID-19 related research, and business. Most indicate the benefit of exploring digital therapeutics and DCTs.

One example from InteropEHRate's own work is put under the spotlight in Box 1.

2.1 Digital therapeutics

Based on the definition from the Digital Therapeutics (DTx) Alliance, digital therapeutics "*delivers medical interventions directly to patients using evidence-based, clinically evaluated software to treat, manage, and prevent a broad spectrum of diseases and disorders*".[14]

DTx technological solutions have to comply with the Medical Devices Directive (MDD)[15], which has been replaced in 2021 by the Medical Devices Regulation (MDR)[16].

In order for DTx to be validated, clinical trials are required. Since they are based mainly on the remote follow-up of patients, trials on DTx – together with those evaluating Health Technology Assessment – are ideal for **DCTs' study design**.

2.2 Rare diseases and orphan drugs trials

Rare diseases and orphan drugs trials are use cases that can also benefit from DCTs. Due to the scarcity of available cohorts of patients with rare diseases, it is very challenging to design clinical trials involving patients and new medications. Current practices include data collected from patients' registries run by health systems. However, the centrally-based design of such registries is often challenging as far as data collection, follow-up, and data exchange are concerned.

An innovative approach to dealing with these challenges is one **DCT trial design that is based on crowdsourcing of data**. With the crowdsourcing approach, relevant data can be collected from patients who are interested in offering their own data for research purposes and who can do so via handheld devices that are connected to their electronic medical record (EMR).

2.3 Treatments and studies based on patient-reported performance indicators

A patient-reported outcome (PRO) is a health outcome that is reported directly by the patient who has experienced the outcome, and not by a health care professional (whether a nurse, doctor, or researcher). These measures (i.e., patient-reported outcome measures (PROMs))

[14] Digital Therapeutics: https://dtxalliance.org/understanding-dtx/

[15] Medical Device Directive: https://ec.europa.eu/growth/single-market/european-standards/harmonised-standards/medical-devices_en

[16] Medical Device Regulation: https://ec.europa.eu/health/md_newregulations/overview_en

are the basis of assessment in some types of conditions (used, for instance, by NHS England).[17]

The use of digitised PROs or electronic patient-reported outcomes (ePROs) is on the rise in contemporary health research settings.[18] Indeed, study designs that use handheld touchscreen-based devices have become the mainstay for remote ePROs' data collection in clinical trials. The conventional approach in this type of study is to provide study subjects (i.e., the patients/citizens) with a handheld device, which operates a device-based proprietary software program. An emerging alternative for clinical trials is called 'bring your own device' (BYOD), which implies that it is the patient himself or herself who provides the actual device (e.g., they use their own smartphone). **InteropeEHRate advocates smartphone-based data collection for DCTs**.

Box 1. Case study on InteropEHRate pilot services in Italy

To validate the InteropEHRate platform for research, a prospective, multicentre, observational study will take place in Italy. It is called INTERVAL (INTERopehrate VALidation).

This study will exemplify how InteropEHRate is contributing to the digital evaluation of drugs and patient-reported outcomes (PRO) collection and management.

For the purpose of this study, the patient's eligibility criteria will be a history of hypertension, a therapy with anti-hypertensive drugs, and the ability to provide informed consent. Eligible patients will receive a notification on their dedicated smart electronic health record (S-EHR) app. Once the informed consent has been obtained, study investigators will be able to ask for data from patients' S-EHR app(s).[19]

On enrolment, patients will be asked to fill out a questionnaire (that captures their PROs) on the perceived side effects of anti-hypertensive medications and will be able to share clinical information produced by healthcare providers. The feasibility and ease of use of data transfer from patients' S-EHR app(s) to the study investigators will be assessed by means of two different questionnaires that are completed by both patients and investigators.

The relative number of patients with data available on arterial blood pressure and anti-hypertensive medications with possible side effects will be calculated. The prevalence of reported side effects will be assessed, and the association between each side effect and disease/patients' characteristics will be investigated. In applying **a DTx validation approach**, study investigators will compare the expected side effects with those actually reported via the S-EHR.

[17] https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/patient-reported-outcome-measures-proms

[18] https://eithealth.eu/news-article/eit-health-living-labs-and-test-beds-programme/

[19] For the purpose of INTERVAL, the following data will be collected: age and gender; year of hypertension diagnosis; latest blood pressure measurement; latest creatinine value; latest left ventricular ejection fraction and interventricular septum thickness at echocardiogram; concomitant medication.

2.4 COVID-19 pandemic research

The 2020-2021 COVID-19 pandemic has often led to innovative responses that have emerged as solutions to several of its key challenges, and particularly to an increase in DCTs and data donation initiatives. Three examples related to apps, data, and DCTs, follow.

At the beginning of April 2020, the German Robert Koch Institute launched the country's official Corona Data Donation App.[20] Since then, more than half a million German inhabitants have donated their health data, in order to contribute to research for a better understanding of the spread of the COVID-19 pandemic.[21]

DCT trial design was also used to test new treatment regimens that needed limited physical contact with patients that took place across several continents include North America and Europe (e.g., the ColCorona clinical study).

2.5 Beyond the research community and towards business

DCTs have moved beyond the research community. They are now perceived as a business opportunity by some organisations.

According to a 2021 survey conducted by GlobalData[22], the majority of firms in the pharmaceutical and healthcare industry anticipate that the costs of DCTs will be lower than traditional trials. The survey found that 50% of clinical/ investigator sites expect the cost of trials to be lower, while 40% of the respondents believe the costs would remain the same. Only 10% of clinical/ investigator sites said that DCT costs would be higher. Hence, the majority of respondents believe that **DCT costs will go down or stay the same.**

In 2020, Deloitte conducted a survey to assess the use of digital technologies across Europe[23]. The survey describes the digital health technologies that are the most frequently used and considered to be the most helpful across Europe: electronic health records (EHRs) were used by 81% of respondents; e-prescribing by 62%; online access platforms/tools (for primary or hospital care) by 46%; patients apps/wearables by 22%. There were, however, notable variations both between and within countries in the use of these technologies. Nevertheless – given the importance of digital/mobile applications use by patients – these figures present **a promising landscape for the DCT model**.

Real-World Data-based research is also a growing sector that indicates business opportunities. A 2016 White Paper from Quintiles IMS (now IQVIA) was entitled "*Breaking New Ground with RWE: How some pharmacos are poised to realize a $1 billion opportunity*"[24]. Five years ago, it estimated that shaking free of traditional thinking on evidence-gathering, and making meaningful, wise investments in RWE could capture dramatic, sustained value – even

[20] http://www.corona-datenspende.de/

[21] https://corona-datenspende.de/science/en/

[22] Pharmaceutical Technology. Industry expects DCT costs to be lower compared with traditional trials: Survey. 8 March 2021. https://www.pharmaceutical-technology.com/surveys/industry-expects-dct-costs-to-be-lower-compared-with-traditional-trials-survey/

[23] Deloitte. Digital transformation. Shaping the future of European healthcare. September 2020.

[24] QuintilesIMS. Breaking New Ground with RWE: How some pharmacos are poised to realize a $1 billion opportunity. 2016. https://www.iqvia.com/-/media/quintilesims/pdfs/qims_breaking_new_ground_with_rwe_whitepaper.pdf

as much as US$1 billion annually – for each of the largest pharmaceutical companies. **DCTs are just one element of a range of business opportunities** in the field of data collection and processing. InteropEHRate is also exploring these options.

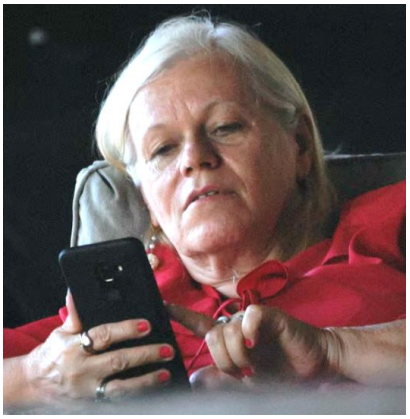
InteropEHRate works in five areas that have a focus on DCTs. In 2022, the project is undertaking a study in Italy that will contribute to research in DTx and the collection and management of PROs on the effects of hypertension medication.

3. The InteropEHRate solution and exploitable outputs

The InteropEHRate vision for collecting data for research is to enable citizens to share health data with research centres without a direct intermediary and directly from their own smartphone.

This section of the White Paper illustrates the data sharing process from an individual viewpoint, through the illustration of a use case – Eve, and goes on to describe the expected project outputs and outcomes as well as the InteropEHRate research scenario workflows.

Box 2. Eve: a fictional use case



The research centre of the Regional University Hospital is conducting a research study about the incidence and risk factors in the general community for a specific medical condition (in this case, hypertension). The research protocol requires two sets of data to be collected: the prospective collection of anonymised health data for two years after the patient's enrolment, and a five-year retrospective evaluation of her data before enrolment.

Eve is a patient with chronic hypertension. She has learned through a promotional campaign (e.g., from a flyer she picked up in the waiting room of her family doctor) that her regional university hospital is conducting a study called "Side effects from hypertensive medication study", which is based on the InteropEHRate format.

Eve is already using a S-EHR app. Thanks to the QR code on the flyer that offers information about the study, she finds out more detail about the research and in particular the kind of data requested for it. Eve is an altruistic person, so she wants to find out more about this data sharing approach. The S-EHR mobile app tells her that the study will compare the health data stored by her app with the enrolment criteria on medical side effects.

After a positive match by the study organisers is made with Eve's own clinical history, she accepts the invitation from the "Side effects from hypertensive medication study", and she signs the consent form with her smartphone. The research protocol requires her to share the health data from her previous five years of treatment and for the next two years. The use of this health data is restricted to the specific research protocol. Eve is asked to fill out a questionnaire on her self-reported side effects from anti-hypertensive medications.

A few months later, Eve complains of nausea probably related to the resumption of her anti-hypertensive medications. Eve opens up her S-EHR app and accesses the questionnaire of the research protocol, filling it out with her symptoms. The questionnaire is sent to the university hospital conducting the research. If the nausea does not disappear, Eve will withdraw her participation in the research study (which she can, in fact, do at any time).

In the event of a patient, such as Eve, withdrawing from the study, the Research Centre of the University Hospital is notified of the fact.

To enable the imagined Eve use case to take place in real life, InteropEHRate has developed a research scenario, a list of the components that the project will deliver, and a set of workflows. The project's research data sharing protocol and its demonstrator implementations are outlined in Figure 1 and Box 3.

3.1 Description of the research scenario

The research scenario describes the relationships between countries that are doing collaborative research (Figure 1). It shows how the various research centres coordinate their activities and what the Reference Research Centre(s) do. The focus is on the sharing of health records and publishing of protocols. From the patient side, it indicates how the S-EHR app handles the checking of enrolment criteria and the signing of consent.

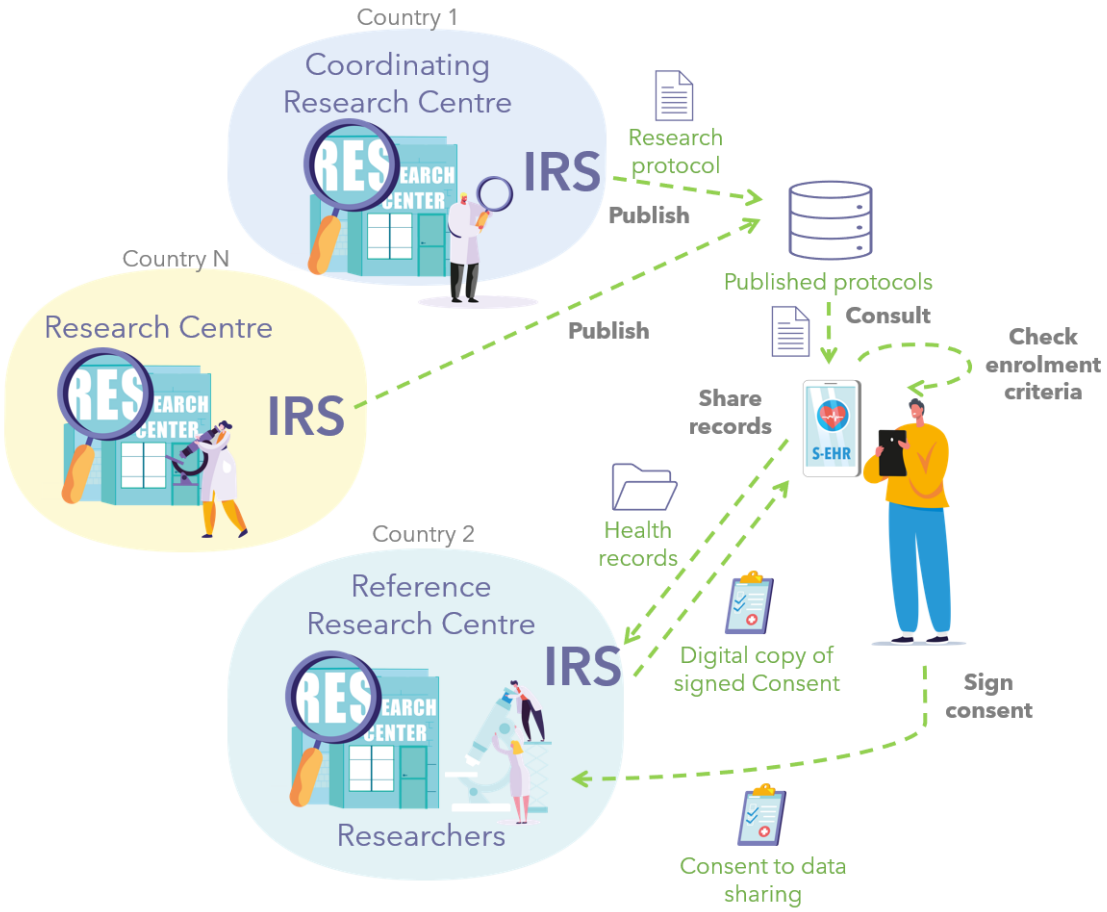


Figure 1. InteropEHRate Research Scenario

Box 3. What InteropEHRate delivers

InteropEHRate delivers **two outputs**: a research data sharing protocol and a set of demonstrator applications.

The **Research Data Sharing Protocol** that defines how, using their S-EHR App, citizens:

- get informed about research studies
- are checked for eligibility
- give or revoke consent on a study-by-study basis
- share their health data anonymously.

InteropeEHRate has various **demonstrator** implementations that function both within the S-EHR app and the Research Network:

- within the S-EHR App:
  - download of research study descriptions
  - citizen involvement (getting informed, handling consent)
  - eligibility check and data retrieval
  - anonymisation, pseudonymisation, security mechanisms.
- within the Research Network:
  - upload and publishing of research study descriptions
  - reception of anonymous citizen data
  - management of pseudonyms.

These outputs are followed by a list of the five **outcomes** that will result from the InteropEHRate project by the end of 2022.

3.2 List of InteropEHRate components

Five components are the outcomes resulting from the InteropEHRate project research scenario:

1. A **set of conformance levels for S-EHR mobile apps** ensure citizens to store securely health data on smart devices (e.g., smartphones) and exchange these by means of a set of InteropEHRate open protocols. One of these data sharing protocols is the Research Data Sharing (RDS) protocol. This protocol is under the citizen's control (i.e., the person who decides what to exchange, with whom, and when), compliant with specific security constraints.

2. **Research Data Sharing (RDS) protocol** is a secure information technology (IT) communication protocol (and related application programming interfaces (APIs)) for publishing and retrieving machine processable descriptions of research studies. They send the citizen's consents and health data from the person's S-EHR Apps to research centres that act as **RDS nodes**, without an intermediary and directly from their smartphone.

3. The **libraries** providing a reference implementation of the RDS protocol and a set of **FHIR profiles**[25] **and FHIR Implementation Guides**.

4. **InteropEHRate Research Services (IRS)**: these services are a prototype of a Research Interoperability Service. The service is a component that interoperates with any S-EHR, by using the research data sharing protocol. This enables researchers to engage volunteer citizens at a cross-national level in new research trials or in retrospective studies, and to receive health data from them. It produces data that may be exploited by the software applications (e.g., in a Clinical Trial Management System) in a research centre.

5. A **reference implementation** of the S-EHR mobile app and the RDS node.

[25] FHIR profiles: https://www.hl7.org/fhir/profiling.html

3.3 InteropEHRate Research Scenario workflows

How the five components identified in Section 3.2 interact with each other and also with patients and study investigators is described in this section.

Clinical data owned by a patient and collected during healthcare processes involving the patient as a subject, can be shared by the patient for different research purposes (Figure 1).

Citizens and researchers may decide to participate in the InteropEHRate Open Research Network. This is a network of research organisations (hospitals, universities, research centres or institutes) that exploit a common IT infrastructure implementing the communication protocol for Health Data Sharing for Research defined by the InteropEHRate project.

The Open Research Network enables the participating researchers to enrol citizens in their research studies (described by specific research protocols) and collect health data for the studies directly from the citizens who have enrolled. The researchers share a common vocabulary, defined by the InteropEHRate profiles and used to refer to any health data required by the research studies that are conducted.

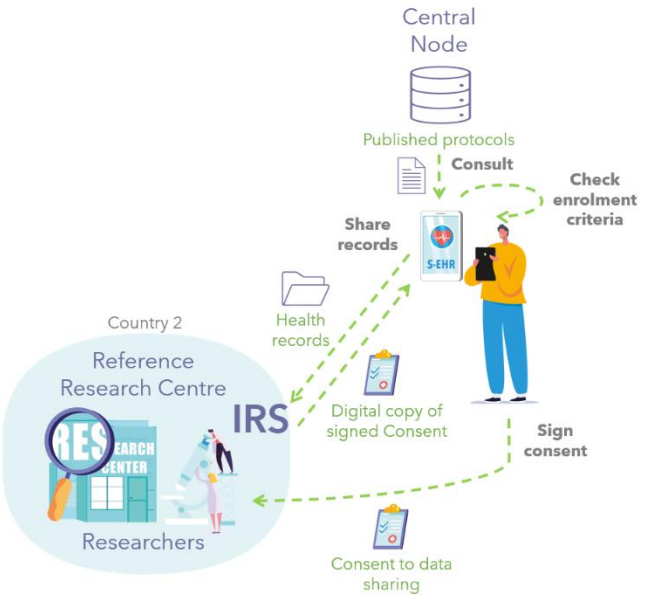
In the following boxes (Boxes 4, 5, and 6), the main InteropEHRate Research Services (IRS) displayed in Figure 1 have been curated in three parts. The content of each box is described briefly ahead of the portrayal of each box.

Box 4 describes the Research Document Services scope of the InteropEHRate platform.

Box 4. Research protocol scope

The RDS protocol concentrates on communication with the citizen's mobile device through six steps:

1. **OPT-IN** to notifications about future studies
2. **DOWNLOAD** of the description of new studies
3. **ENROLMENT** into a new study
4. **DATA RETRIEVAL** from the mobile device
5. **WITHDRAWAL** from study
6. **OPT-OUT** from future studies



Other aspects of the research process (how to define a study and how to work with an ethical committee) are not covered.

Box 5 describes the Research Definition Document Interface (RDDI) of the platform.

Box 5. RDDI - Interface for downloading research definitions

There are three operations enabled by the RDDI interface:

1. The S-EHR App regularly polls the central node of the Research Network for new studies.
2. Digitally signed Research Definition Documents (RDD) are automatically downloaded.
3. The eligibility of the citizen regarding the study criteria is checked by the S-EHR App (based on citizen consent).

Finally, Box 6 describes the Research Services Interface (RSI).

Box 4. RSI - Interface for sharing health data for research

The interface for sharing health data for research support four steps of the RDS protocol:

1. The citizen decides whether to participate in the study and selects a reference research centre.
2. The digitally signed consent is sent to the reference research centre.
3. During the study, at regular intervals defined by the RDD, relevant health data are automatically retrieved, anonymised, and sent to the reference research centre.

4. The citizen may withdraw from a study at any time and may opt out from the research altogether.

4. Critical points left for research organisations to address

Clinical research is a complicated field, which is strictly regulated and requires both time and resources. Clinical project operations management is the cornerstone of effective clinical trials. Management is a vital component of all types of clinical research trials, whether a research team is working on a single-site Phase I study or a multi-site Phase III trial and includes various stages and aspects as presented in Figure 2.[26]

Figure 2. Stages and aspects of clinical project management

Clinical trials generally consist of various phases. Many clinical research studies are assisted by a Clinical Research Organisation (CRO). CROs offer professional services to research teams, both in Europe and at an international level.[27] Although different types of CROs exist – each with a different level of specialisation – a typical CRO's services covers at least ten domains: regulatory affairs, site selection and activation, recruitment support, clinical monitoring, data management, logistics, pharmacovigilance, biostatistics, medical writing, and project management, among other services.

The InteropEHRate platform is able to integrate and support research and CROs in some specific domains, such as a patient's enrolment and data collection management. The platform also offers alternatives to data collection through the crowdsourcing of patients' data.

[26] http://www.nexuscro.com/wp-content/uploads/2015/11/

[27] https://www.eucrof.eu/

It is not, however, the role of InteropEHRate Research Services to cover tasks related to, for example, acceptance of a research proposal by an ethical committee, data aggregation and preparation, research data analytics, or management of the research process.

More precisely, InteropEHRate Research Services (IRS) address six key challenges:

- **Formal description of a research study** through a FHIR-based Research Definition Document.
- **Automatic check of eligibility** to studies using health data on the mobile device.
- **Informed consent** by the citizen on a study-by-study basis.
- **Cross-border data collection** due to FHIR-based semantic data representation.
- **Secure and digitally signed** data transmission.
- **In-phone data anonymisation** methods.

In summary, InteropEHRate can assist CROs or research centres in achieving a significant reduction in the amount of time and resources required in traditional patients' recruitment and PROs collection and administration.

5. Conclusions

Decentralised clinical trials are becoming an effective approach thank to the increased capacity to collect real-world health data shared by patients.

InteropEHRate enables a citizen-centric health data approach that can accelerate clinical research in general and boost innovation. The InteropEHRate vision for collecting data for research is to enable citizens to share health data with research centres without a direct intermediary and directly from their own smartphone.

Specifically, the focal research areas are the fields of digital therapeutics, rare diseases and orphan drugs, and COVID-19 related research. As InteropEHRate advocates for smartphone-based data collection, it also facilitates the incorporation of patient-reported outcomes.

Through the research scenario, InteropEHRate has developed a platform of technical solutions to support research centres and CROs. This platform will be validated in the project INTERVAL, a prospective, multicentre, observational study that will take place in Italy in 2022, contributing to research in digital therapeutics and patient-reported outcomes collection and management on the effects of hypertension medication.

The InteropEHRate platform consist of a research data sharing protocol and a set of demonstrator applications. This platform includes a set of conformance levels for S-EHR mobile apps, the Research Data Sharing (RDS) protocol, the libraries required for implementing the RDS protocol and a set of FHIR profiles, InteropEHRate Research Services (IRS) and a reference implementation of the S-EHR mobile app and the RDS node.

InteropEHRate research services included in the platform are the Research Document Services, the Research Definition Document Interface (RDDI) and the Research Services Interface (RSI). These research services address the challenge of formal description of a research study through a FHIR-based Research Definition Document, automatic check of eligibility to studies using health data on the mobile device, informed consent by the citizen on a study-by-study basis, cross-border data collection due to FHIR-based semantic data representation, secure and digitally signed data transmission, and in-phone data anonymisation methods.

The InteropEHRate platform is able to integrate and support research and CROs in some specific domains, such as a patient's enrolment and data collection management, and crowdsourcing of patients' data, achieving a significant reduction in the amount of time and resources required in traditional patients' recruitment and PROs collection and administration.

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