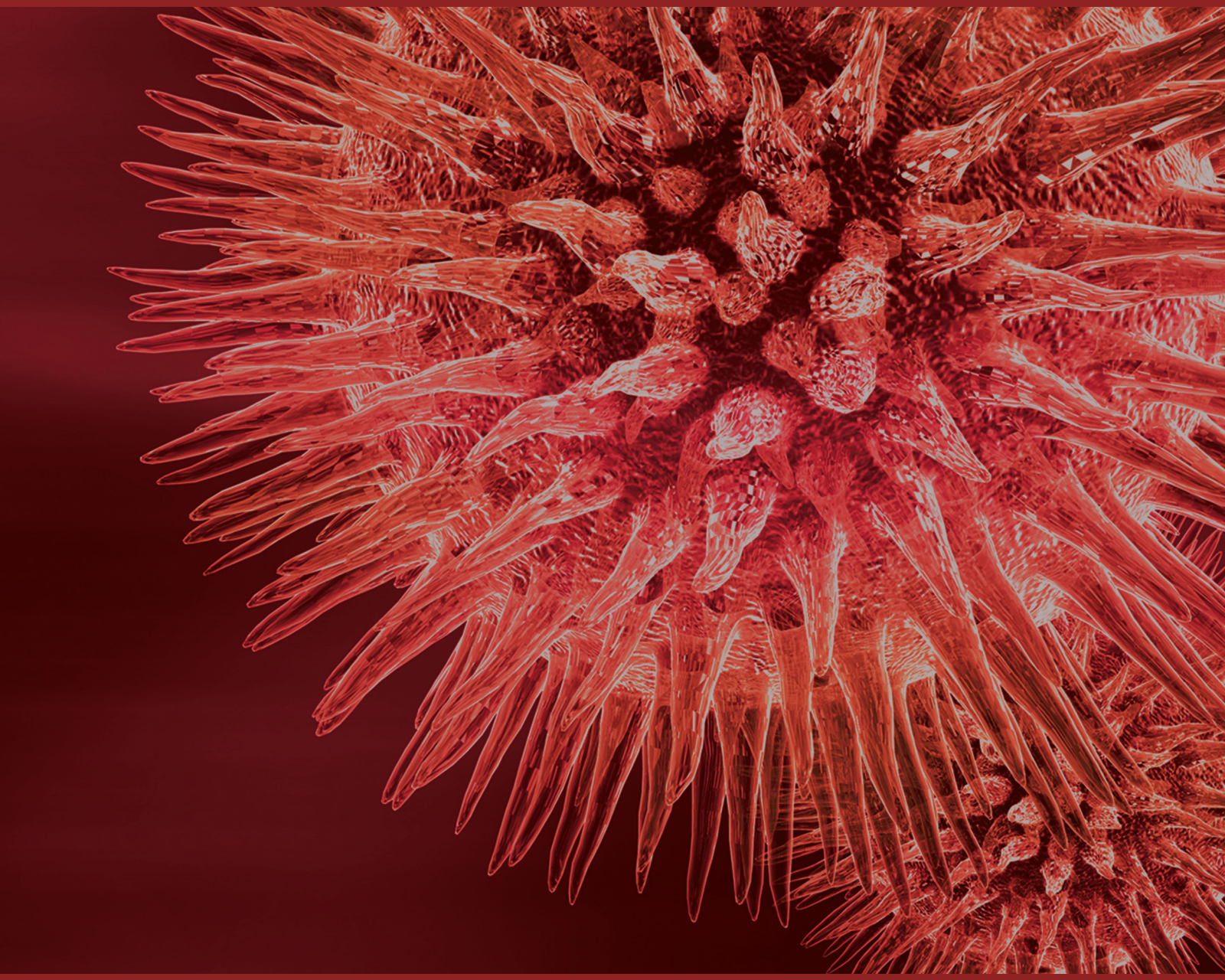
BioMed Research International

Improving Performance of Clinical Research: Development and Interest of Electronic Health Records

Guest Editors: Ariel Beresniak, Danielle Dupont, Mats Sundgren, Dipak Kalra, and Georges J. E. De Moor



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Editorial

Improving Performance of Clinical Research: Development and Interest of Electronic Health Records

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Collecting health information from patients is probably one of the most ancient medical acts. The Hippocratic Corpus was a compendium of medical records from Ancient Greece and one of the first attempts to classify diseases according to symptoms and observations.

Over the years, health records have been mainly used in paper format to document individual patient characteristics, to keep track of treatments, and to report patient outcomes. Nowadays, as medical care is getting more and more complex and personalized, the recent advances and uses of information technologies enable capturing, processing, storing, and mining patient-level data in order to quickly extract meaningful clinical information and medical knowledge for clinical decision making and to further personalize health care. With their widespread use, Electronic Health Records (EHRs) have become a very important tool from which new services can be provided. This major breakthrough is already starting to transform research and development of innovative health products by enhancing and speeding up existing processes. This is because EHR data can be used to rapidly optimise clinical protocol designs, to better identify and faster recruit eligible patients for clinical trials, and to foster new, efficient ways of collecting data during clinical study conduct and improve the detection and reporting of serious adverse events.

Despite available technologies, numerous challenges remain which still require significant efforts and time: ethical, legal, data privacy issues, information technology systems integration, optimal interoperability for a seamless and trustworthy data exchange, and so forth.

Importantly, major innovations such as developing best in class and seamless EHR-enabled clinical data exchange systems require building awareness and trust with multiple stakeholders in order to maximize the expected benefits, as well as societal acceptance from patients, health care providers, governmental bodies, and clinical trial sponsors. In particular, clinical research investigators and sponsors have long been using conventional clinical research processes that rely more upon ad hoc case finding and ploughing through large numbers of paper records. They will thus require special attention, including the development and dissemination of customized value propositions that explain and evidence innovative EHR-based clinical research platforms, how these compare with existing practices, and which qualitative and quantitative benefits they can deliver in order to facilitate adoption and large scale implementation.

EHRs offer an unprecedented opportunity, as well as technological challenges, to change the current clinical research paradigm, including the following:

(1) Patient databases are growing rapidly and are becoming more accessible.

(2) The diversity of health records is important, covering all kinds of populations and health conditions.

(3) EHRs are heterogeneous, which makes interoperability (seamless data exchange) and integration of information a challenging task.

(4) For a particular reuse of EHRs, only a selection of key parameters (data items) might be useful for clinical research.

(5) EHRs are dynamic: the monitoring of the changes could become important features for many research applications.

(6) The use of EHR data for clinical research could speed up the patient recruitment phase, reduce the number of protocol amendments, improve the efficiency of major parts of the clinical trial process, and reduce costs.

(7) EHRs offer many opportunities for data mining, such as to extract original meaningful information from a large set of patients or populations.

Given the growing demand worldwide for clinical evidence (including from real-world contexts), as well as the formidable challenges in clinical research today (including costly protocol amendments, significant delays in patient recruitment, time-consuming and redundant clinical data entry in appropriate data management systems, and the escalation in research and development costs), the question is not so much if clinical research will use these new concepts in current practice and benefit from reusing EHR data, but when.

As more and more applied research domains are now exploring how to use electronic platforms to facilitate key clinical research tasks, and considering the inexorable trend towards modernising clinical research models to create, deliver, and capture more value and benefits, it appears to be good timing to provide a scientific overview on the most advanced research and developments in this field in the frame of a special issue.

This special issue provides an opportunity to present the latest scientific contributions and technological developments in this emerging field that can be derived from the research use of EHR data.

The objectives of this special issue are twofold:

(1) For the first time, to bring together and to present some of the latest research and development efforts in this field, including technological R&D, surveys, and pilot studies.

(2) To support more and focused research activities in this domain. Given the large number of clinical trials worldwide, the next challenge will naturally be to ensure a seamless and sustainable deployment of these advanced and trustworthy interoperable platforms in order to enable the reuse of EHR data at the global level.

There is no doubt that the original articles published in this special issue already evidence this emerging reality for the future of clinical research, thanks to the contributions of a broad number of highly experienced and specialized authors in this field. The presented articles address a wide range of perspectives and compile the most promising research findings and the latest developments.

As EHRs will continue to have a significant and positive impact on state-of-the-art clinical development, we are confident that this special issue will stimulate further ideas and research for enhancing, speeding up, and optimising clinical research worldwide, towards delivering effective and safe innovative medicines to health care faster, to the benefits of patients, the entire health systems, and society.

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Research Article

Postmarketing Safety Study Tool: A Web Based, Dynamic, and Interoperable System for Postmarketing Drug Surveillance Studies

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Postmarketing drug surveillance is a crucial aspect of the clinical research activities in pharmacovigilance and pharmacoepidemiology. Successful utilization of available Electronic Health Record (EHR) data can complement and strengthen postmarketing safety studies. In terms of the secondary use of EHRs, access and analysis of patient data across different domains are a critical factor; we address this data interoperability problem between EHR systems and clinical research systems in this paper. We demonstrate that this problem can be solved in an upper level with the use of common data elements in a standardized fashion so that clinical researchers can work with different EHR systems independently of the underlying information model. Postmarketing Safety Study Tool lets the clinical researchers extract data from different EHR systems by designing data collection set schemas through common data elements. The tool interacts with a semantic metadata registry through IHE data element exchange profile. Postmarketing Safety Study Tool and its supporting components have been implemented and deployed on the central data warehouse of the Lombardy region, Italy, which contains anonymized records of about 16 million patients with over 10-year longitudinal data on average. Clinical researchers in Roche validate the tool with real life use cases.

1. Introduction

It is a well-accepted fact that, due to the limited scope and duration of clinical trials, drugs may still have serious side effects, adverse drug reactions (ADRs), after they are marketed. Postmarketing drug surveillance systems have been in place in order to analyze additional information about a drug's safety, efficacy, and optimal use to capture such ADRs. During the last decades, postmarketing activities in pharmacovigilance have largely depended on spontaneous case reports, which is still the case unfortunately. There are certain limitations on surveillance activities with spontaneous report data [1–4]. Postmarketing surveillance is also of vital importance for pharmacoepidemiology, especially for evidence development about effectiveness, safety, and quality of drugs in terms of ADRs [5, 6].

At present, postmarketing drug surveillance is largely being carried out with traditional methods for both pharmacovigilance and pharmacoepidemiology. In pharmacovigilance, there is active research on data mining algorithms [7] running on spontaneous report databases. On the other side, dedicated cohort and case-control studies are being performed within pharmacoepidemiological research. Although these traditional methods are currently dominant, a new research area that uses the already available electronic health data for clinical research purposes is emerging, which is referred to as the secondary use of Electronic Health Records (EHRs). EHRs provide a huge, but still underutilized, source

of information on the real world use of drugs for observational studies. Although EHRs are primarily designed for patient care, they also contain a broad range of clinical information highly relevant to surveillance studies. EHR data available in clinical care systems can clearly complement and strengthen existing postmarketing safety studies [3, 8, 9]. Relative to spontaneous reports, EHRs cover extended parts of the underlying medical histories, include more complete information on potential risk factors, and are not restricted to patients who have experienced an adverse drug reaction.

Successful utilization of available EHRs for clinical research in terms of access, management, and analysis of patient data within and across different functional domains is a critical factor in terms of secondary reuse [9]. In line with this vision, there are important efforts for building large data pools from the EHRs to benefit from the available longitudinal observational data. The Sentinel Initiative of the U.S. Food and Drug Administration (FDA) aims to build a distributed network for active postmarketing surveillance for drug safety in the USA [10, 11]. The Observational Medical Outcomes Partnership (OMOP) is another important initiative targeting a similar objective for improvements in postmarket drug monitoring [12]. There are several other pharmacoepidemiological databases such as the Clinical Practice Research Datalink (CPRD) [13] which is based on the General Practice Research Database (GPRD) experience in the UK and The Health Improvement Network (THIN) database containing longitudinal medical data [14]. As a natural result, data mining on such national and international data pools appears as a new research area for signal detection and safety monitoring [3, 4].

The objective of the aforementioned initiatives is to use the available EHR data held by multiple different systems for clinical research purposes (mainly for postmarketing surveillance, comparative effectiveness research, and evidence development). In addition to the distributed architecture of the Sentinel Initiative, recent research projects like SALUS (Scalable, Standard based Interoperability Framework for Sustainable Proactive Post Market Safety Studies) [8], TRANSFoRm (Translational Research and Patient Safety in Europe) [15], and EHR4CR (Electronic Health Records for Clinical Research) [16] address the different levels of the interoperability problem between the clinical research and patient care domains with a distributed perspective.

Current research on postmarketing surveillance for pharmacovigilance and pharmacoepidemiology tries to unify the available EHR data on a common information model. Most of the time, this forces the EHR systems to implement the necessary adapters for transforming data into the defined common model and persist in a separate database. Either distributed or not, analyses on longitudinal EHR data require clinical researchers to implement the designed algorithms and build methods according to the predefined data model of the database that they are working on. On the other hand, some approaches transform the query to the native data model at each transaction. It is an experienced fact that data and processing requirements of different areas of clinical research change in time while the quality, quantity, and availability of EHR data on patient care side increase. In parallel with this, new initiatives propose new common data models into which collaborating EHR sources have to transform and transfer data, regardless of the system's nature. The literature exemplifies this situation clearly.

Vaccine Safety Datalink [17] is an early initiative for transforming EHR data for postmarketing safety surveillance of vaccines. FDA's Sentinel Initiative and the Mini-Sentinel pilot system [10, 11] are one of the latest and important efforts for postmarketing surveillance, built on the experiences of Vaccine Safety Datalink. Mini-Sentinel builds a distributed system to answer safety queries of clinical researchers through a common information model. OMOP [12] introduces its own common data model (CDM) to transform EHR data. Informatics for Integrating Biology and the Bedside (i2b2) [18] is another parallel effort with similar objectives that exposes its own common information model. CPRD [13] is a European example of the latest pharmacoepidemiological databases and there are several ongoing projects supported by European Medicines Agency and European Commission using a common information model for surveillance activities. The fact is that those common information models are not so "common"; they are only used within the boundaries of the associated initiatives and projects.

In this paper, we address the heterogeneity problem among common data models for clinical researchers who work on EHR data for postmarketing surveillance studies. We show that this problem of interoperability can be solved in an upper level with the use of common data element (CDE) phenomenon [19]. If the applications share the machine-processable definitions of the data elements and there are established links between data elements of different domains (i.e., clinical research and patient care domains), this can be used to facilitate automatic access to data across different domains. Hence, in the context of postmarketing surveillance, uniform observational analysis methods can be designed and implemented independently of the underlying data model, whether the source is a pharmacoepidemiological database or directly a hospital information system.

In the light of the common data element based interoperability approach, we design and implement the Postmarketing Safety Study Tool (PMSST) which can extract any needed information from a patient record after it is retrieved as a result of an eligibility query or it is directly accessed from the EHR database within a data mining routine. Our design is built upon the notion of CDEs and makes use of a Semantic Metadata Registry (MDR) to retrieve data element definitions and use their extraction specifications to access data [19, 20]. With the use of the extraction specifications, PMSST lets the researcher define what needs to be extracted from the patient records with the help of the abstract CDE definitions accessed from a semantic MDR [19]. With this dynamic behavior, the researcher writes her methods on the schema/template which will be created based on the data elements that she manipulates. With the help of the underlying interoperability framework [19], postmarketing surveillance methods do not have to be restricted to the data model of an EHR source.

2. Materials and Methods

The tool that we introduce in this paper has been built within the SALUS interoperability framework. Hence, first of all, SALUS project and its incorporated common data element based interoperability framework are introduced in Section 2.1. Afterwards, Section 2.2 outlines the general design principles of the PMSST on top of a use case scenario from the SALUS project. And Section 2.3 describes the implementation and finalizes the Materials and Methods.

2.1. SALUS Project. SALUS aims to create a semantic interoperability layer in order to enable the secondary use of EHR data for clinical research activities. SALUS follows a common data element based interoperability approach and uses the semantic MDR to maintain its common data elements (CDEs). Built upon its abstract CDE definitions, SALUS exposes a semantic RDF [21] based content model as its common information model. SALUS project deals with different content models both in clinical care (i.e., HL7/ASTM CCD [22] and CEN/ISO 13606 [23]) and clinical research domains (i.e., SDTM [24] and OMOP CDM [12]) and harmonizes them in the SALUS common information model (CIM) [25]. Through its semantic interoperability layer, SALUS accepts eligibility queries and returns resultant patient summaries as instances of SALUS CIM.

Several organizations are publishing common data element dictionaries and common models in order to solve the interoperability problem within and between clinical research and patient care borders. The objective is to provide a dictionary like the collection of the abstract definitions of common data elements. Most of the time, these definitions are published as unstructured text files. Rarely, semistructured spreadsheets are used to publish the data element specifications. Health Information Technology Standards Panel (HITSP) is one of such organizations publishing a library of common data elements, called HITSP C154: Data Dictionary [26]. One CDE from this dictionary is "Conditions Problem Code" which is defined as the code describing the medical problem according to a specific vocabulary of problems. This abstract CDE definition can be bound to an implementation such as HL7/ASTM CCD with an XPath script as in the following snippet:

```
/cda:ClinicalDocument/cda:component/cda:
structuredBody/cda:component/cda:section
/cda:entry/cda:act[cda:templateId/@root
='2.16.840.1.113883.10.20.1.27']/cda:
entryRelationship[@typeCode='SUBJ']/cda:
observation[cda:templateId/@root='2.16.
840.1.113883.10.20.1.28']/cda:value
/@code
```

Data retrieval mechanism of the SALUS enabled clinical research tools has been built on top of the idea of data interoperability through federated semantic metadata registries [27] where the machine-processable CDE definitions play a crucial role. The CDE based data interoperability approach introduces a federated system in which the abstract and machine-processable data element definitions in ISO/IEC 11179 [28] formalism are managed within metadata registries and can be linked/mapped with each other by using semantic web technologies. This approach makes a clear distinction between the abstract definitions and implementation dependent parts of the data elements.

The abstract SALUS common data element (CDE) [29] definitions published in the scope of SALUS project are maintained within a semantic MDR. Each CDE has its extraction specification which can be executed on SALUS CIM conformant patient data to extract the indicated piece of information. The extraction specifications of the SALUS CDEs are SPARQL [30] scripts since SALUS common information model (CIM) is RDF based.

As illustrated in Figure 1, different organizations or standardization bodies can maintain their own CDE specifications inside the semantic MDR architecture and establish the semantic links to other CDEs from other systems or domains. If one abstract CDE set has the access method (so called extraction specifications such as an XPath or SPARQL script) to an implementation specific content model (i.e., XML based HL7/ASTM CCD or RDF based SALUS CIM), the semantic link chain among the CDEs can be traversed in line with the linked data principles and data can be extracted from the instance conforming to that content model pointed by the extraction specification. Compared to static message translation between different specifications, this approach well integrates with the distributed architectures and does not need to perform costly operations such as parsing and message construction. The semantic MDR provides the necessary functionality together with the interfaces so that the users and semantic-aware applications can interact with the system easily.

PMSST is one of the safety analysis tools developed within the scope of the SALUS project. Within this CDE based data interoperability framework, PMSST retrieves the CDE definitions from a semantic MDR where any common data element model can be maintained according to ISO/IEC 11179 metamodel [28]. Study Data Tabulation Model (SDTM) is a standard data model for the pharmaceutical companies while submitting information about clinical studies to FDA. Pharmaceutical companies like Roche use SDTM variables for data annotation during their postmarketing surveillance studies. In our implementation, the registry maintains the SDTM variables and the SALUS common data elements [29], and there are semantic links between SDTM and SALUS data elements as introduced by Sinaci and Laleci Erturkmen [19] and as illustrated in Figure 1.

Using PMSST, a clinical researcher designs a data schema (a template) by using SDTM variables on which she writes scripts (i.e., SAS [31]) for surveillance studies. The system knows how to extract information from the underlying EHR data by using the extraction specifications of the CDEs. Therefore, the researcher is not bound to the data model of the underlying database; it could be a system providing HL7/ASTM CCD [22] based patient summaries or an OMOP

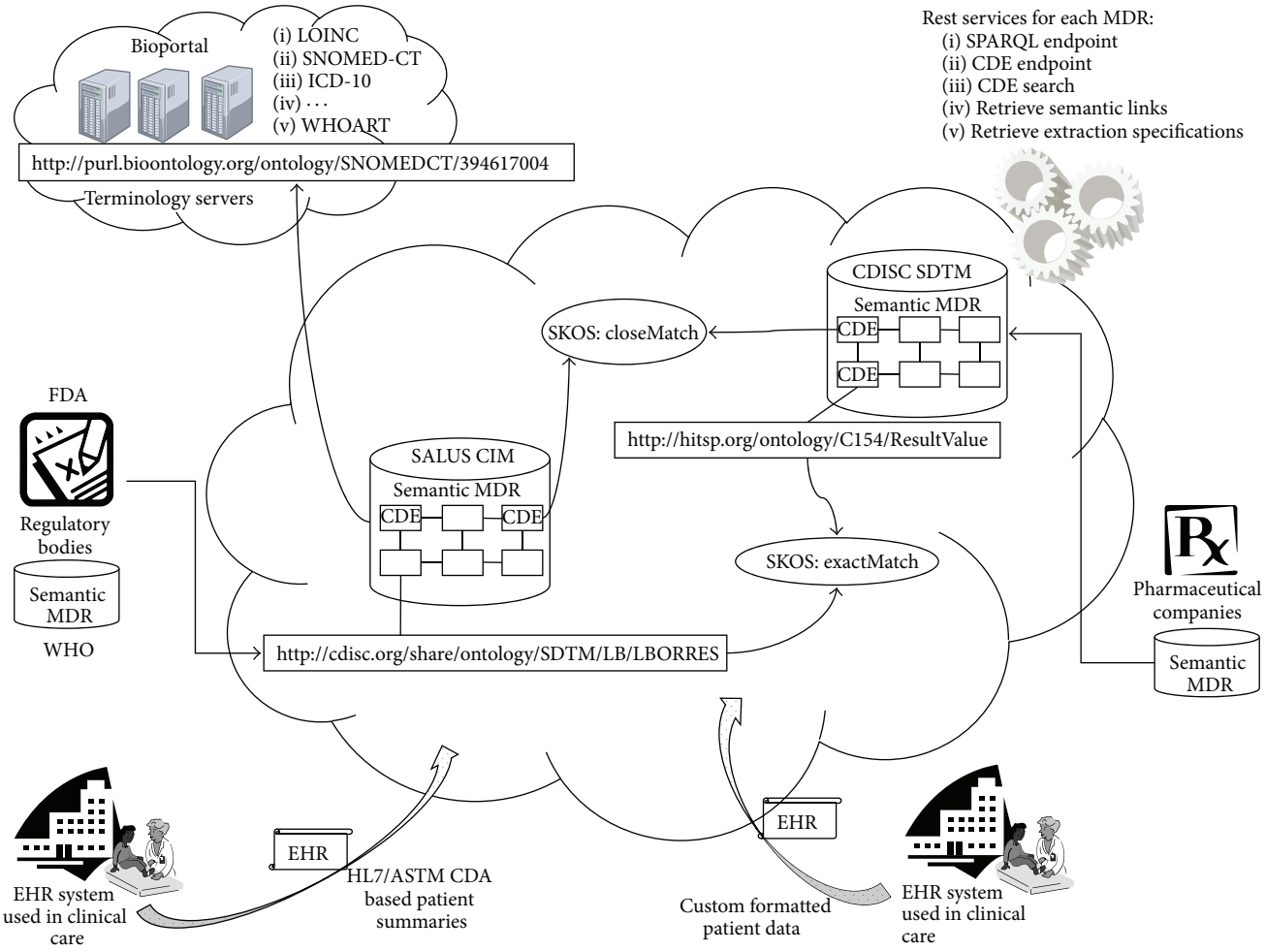

Figure 1: CDE based data interoperability framework through federated semantic metadata registries.

database or any other EHR database as well as a pharmacoepidemiological database. As long as the appropriate extraction specifications (i.e., XPath [32] scripts for HL7 CCD) are available, PMSST can extract the necessary information. The communication with the metadata registry is carried out through an international interoperability profile, namely, IHE Data Element Exchange (DEX) profile [20] in which PMSST implements the metadata consumer role while the semantic MDR implements the metadata source role.

2.2. Design Considerations. Postmarketing Safety Study Tool is a web based tool enabling clinical researchers to extract data from different EHR systems by designing data collection sets through common data elements. After patient record is retrieved as a result of an eligibility query, any needed information can be extracted from the patient record to populate the data collection set with the help of abstract CDE definitions used to annotate data collection set definitions. By means of the underlying interoperability framework [19], PMSST enables researchers to develop analysis method on the data collection set schema defined by abstract CDEs without being concerned about the structure of the underlying data source. The driving force during the design phase of PMSST is a real world use case identified by the pharmaceutical company Roche in the scope of SALUS project.

2.2.1. PMSST Use Case

Background of the Use Case. Congestive heart failure (CHF) is a leading cause of hospitalization for patients aged 65 years and older. CHF is of particular concern in diabetic patients in whom incidence rates are two to five times greater than those in the general population. The United Kingdom Prospective Diabetes Study (UKPDS) estimated incidence rates of 2.3–11.9 cases per 1000 patient-years in diabetic patients. Several risk factors of CHF in diabetic patients have been identified. These include, for example, duration of diabetes, history of ischemic heart disease, renal function, hypertension, diabetes treatments, and HbA1C. However, the incidence of CHF in diabetic patients with a recent acute coronary event is not fully known. In particular, no estimates of CHF for different treatment regimens are available in these patients.

Roche is conducting clinical trials in both acute coronary syndrome (ACS) patients and in ACS patients with diabetes.

Table 1: Data collection set schema details for the PMSST use case.

Scheme item description	Data Elements of the Schema Item	Corresponding SDTM data element name	MedDRA code for MH.MHPTCD
Sex	Sex	DM.SEX	
Date of acute Coronary syndrome (ACS) event	(i) ACS event (ii) Start date of ACS event	(i) MH.MHPTCD (ii) MH.MHSTDTC	10051592
Date of acute myocardial infarction	(i) Acute myocardial infarction (ii) Start date of acute myocardial infarction	(i) MH.MHPTCD (ii) MH.MHSTDTC	10000891
Date of unstable angina	(i) Unstable angina pectoris (ii) Start date of unstable angina pectoris	(i) MH.MHPTCD (ii) MH.MHSTDTC	10002388
Had a congestive heart failure (CHF) before start of ACS (Y/N)	(i) Congestive heart failure (ii) Congestive heart failure time indicator	(i) MH.MHPTCD (ii) MH.MHSTDTC	10007559
Had a CHF after start of ACS (Y/N)	(i) Congestive heart failure (ii) Congestive heart failure time indicator	(i) MH.MHPTCD (ii) MH.MHSTDTC	10007559

Whilst the trials are blind, it is important to compare the observed overall incidence rate of an important adverse event like CHF in the trials with that in similar background populations. Such a comparison provides a context to the observed incidence and enables us to identify any potential safety concerns earlier on (e.g., if the observed incidence in the trial is greater than the background).

Objective. The objective of this use case is to estimate incidence rates of CHF in diabetic patients with a recent acute coronary syndrome (ACS) event considering other diabetic medications of patients such as type 2 diabetes (T2D) and related treatment regimens as well. The estimation results should be stratified based on patient demographics such as age or gender.

Patient Selection. Identify all patients with a first ACS event defined by acute myocardial infarction or unstable angina during the period 2005 to 2011. Include only those patients who have a minimum of 1-year history prior to the ACS. Exclude those patients who died within 30 days after the ACS event. Exclude those patients aged less than 18 at the time of ACS. The remaining patients define an ACS cohort of interest. For each patient, the STARTDATE is set to 30 days after the ACS event (so if a patient has an ACS on 5th July 2007, his start date is set to 4th August 2007). We allow a 30-day delay to ensure the ACS has stabilized. For each patient define the LASTDATE as the minimum of date of death or the date the patient transfers out of the system and can provide no more data, that is, 31st Dec 2011.

Data Collection Set Definition. For the ACS cohort described in the previous section, we identified the necessary data that needs to be gathered as a data collection schema (like a common information model required for this surveillance study) composed of several schema items which can be resembled to the columns of a relational database table. While some of the data collection set schema items can be extracted from the EHR data using the extraction specification of a single SDTM data element, some of them require further calculations. For instance, whilst the start date of the ACS event can be extracted in a single operation, we should take the start date of the ACS event into account to be able to produce the result for "average systolic blood pressure (BP) over 12 months before the start of ACS" schema item; it requires querying of particular measurements within a particular timeframe and calculation of the mean value.

Table 1 shows a sample of the schema items together with the corresponding SDTM data elements. In order to calculate the final results for the schema items, some of the data elements should be provided with specific MedDRA [33] codes to indicate the values according to the requested information which are also indicated in Table 1. For example, "Date of Acute Myocardial Infarction" is described with MH.MHPTCD = 10000891, MHSTDTC = ?.

2.2.2. How the Use Case Affected PMSST Design? Patient selection phase is the execution of the eligibility criteria for retrieving the data of the defined cohort. For PMSST, this execution is handled through the semantic interoperability layer of SALUS. However, this could be any other system like Sentinel or Query Health [34] from which data is retrieved in the form of a content model. The data collection set schema is defined by annotating the schema items with the CDEs that are already being used in research community, in our case SDTM data elements. As long as the extraction specifications of the selected CDEs to that content model are available from the EHR data sources and reachable with appropriate links in the semantic MDR, PMSST can perform the same execution to build data according to the schema defined by the researcher with the help of the CDEs.

Analyzing the use case, we elicited the key requirements for PMSST and based the design of the key functionalities of PMSST on these requirements. During the data collection set schema definition process, values of particular schema items might be used in defining other schema items. Therefore, PMSST provides a flexible variable definition mechanism.

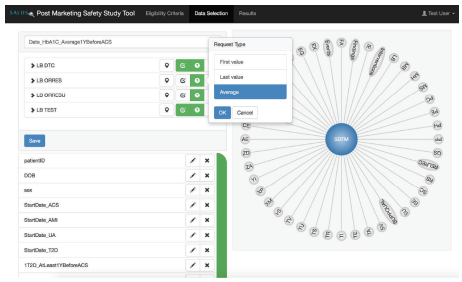

Figure 2: A snapshot of PMSST while the researcher defines a data collection set schema. On the right hand side, domains of SDTM form a circle; if selected, then CDEs of that domain form the circle. On the left hand side, a schema item "Date_HbA1C_Average1YBeforeACS" is created out of 4 SDTM elements. Below that, a list of other schema items is shown.

PMSST keeps track of the variable definitions and generates the queries to be applied on the EHR data and organizes their execution order.

As it can be seen in Table 1, some of the schema items need further calculation such as average value of blood pressure measurements, date of the first occurrence of T2D diagnosis, and last weight value before the ACS event. We design PMSST such that it would present different selection and calculation options automatically considering the value domain of the schema item.

Value domains of the used CDEs may be referring to different terminology/coding systems. For example, while asking whether a patient has T2D or not, researcher at Roche uses MHPTCD common data element from the MH domain of SDTM. Since this data element requires a coded value from MedDRA, the researcher should easily assign values to such data elements during her schema design. For this purpose, PMSST has been integrated with a terminology server so that it would recommend possible values based on the schema item through a type-a-head search mechanism.

2.3. System Description. PMSST is a web based tool which can be used via modern web browsers. It has been implemented with the latest high performance web technologies incorporating HTML5 design principles and RESTful client-server communication. The tool is composed of an eligibility query execution and a data selection part. Details of the former are out of the scope of this paper. Upon the execution of an eligibility query, a cohort of patient data is retrieved in the form of a content model adopted by the EHR sources. We claim that the CDE based interoperability implementation of PMSST can make use of any content model as long as the appropriate extraction specifications are available for the abstract CDE definitions within the semantic MDR framework.

Figure 2 presents the data selection phase of PMSST. The user can define a data collection set schema at this phase by using the CDE definitions retrieved from the semantic MDR. In our implementation, the registry maintains SDTM variables and SALUS CDE set according to ISO/IEC 11179 metamodel principles. When the user decides to use SDTM, the object classes (aka domains) are presented to the user to give a top-down browsing experience. When a domain is selected, the data elements created out of that object class are presented to the user. When a CDE is selected, it appears on the left hand side to create further calculations. Once a schema item is designed, it is saved and the overall schema design continues. The user can edit or delete an existing item anytime during the design phase.

2.3.1. Data Flow between Components. PMSST is composed of several different components among which a number of integration mechanisms exist. In Figure 3 the flow of data between those integrated components is depicted and the steps of the flow are described in as follows.

(1) The researcher uses a web browser to define the data collection set schema by using the CDEs. Roche researchers use SDTM variables in our deployment as identified in Table 1.

(2) CDEs are maintained in the semantic MDR and retrieved through the IHE DEX profile. The user browses the CDEs starting from the object classes in a top-down fashion.

(3) If the user likes to restrict the value of a selected data element (i.e., set acute myocardial infarction to MHPTCD element), possible values can automatically be searched from the terminology server. PMSST knows in which coding system to look for the term by analyzing the value domain of the CDE definition automatically.

(4) After the user completes the schema definition, identifying each schema item by using abstract CDE definitions, the schema definition is sent to the PMSST engine on the server side.

(5) Eligibility query is sent to the SALUS system and EHR data of the eligible patients is retrieved in the form of SALUS common information model.

(6) For each schema item definition, PMSST engine extracts information from the EHR data and performs necessary calculations to place into the appropriate location according to the schema definition.

(6.1) Schema is defined by SDTM elements. Semantic MDR keeps the mappings between SDTM and SALUS CDEs as presented in Table 2 in the next section, and SALUS CDEs have the extraction specifications to access the necessary information from the EHR data. CDE definitions, mappings, and extraction specifications are retrieved from the semantic MDR in conformance to the IHE DEX profile. Since SALUS CIM is an RDF based model, the extraction specifications of the SALUS CDEs are SPARQL scripts.

(6.2) If the schema item definition includes a value in one of its defining CDEs, value analysis should be done. However, in our deployment, EHR data is coded with ICD-9-CM terminology system

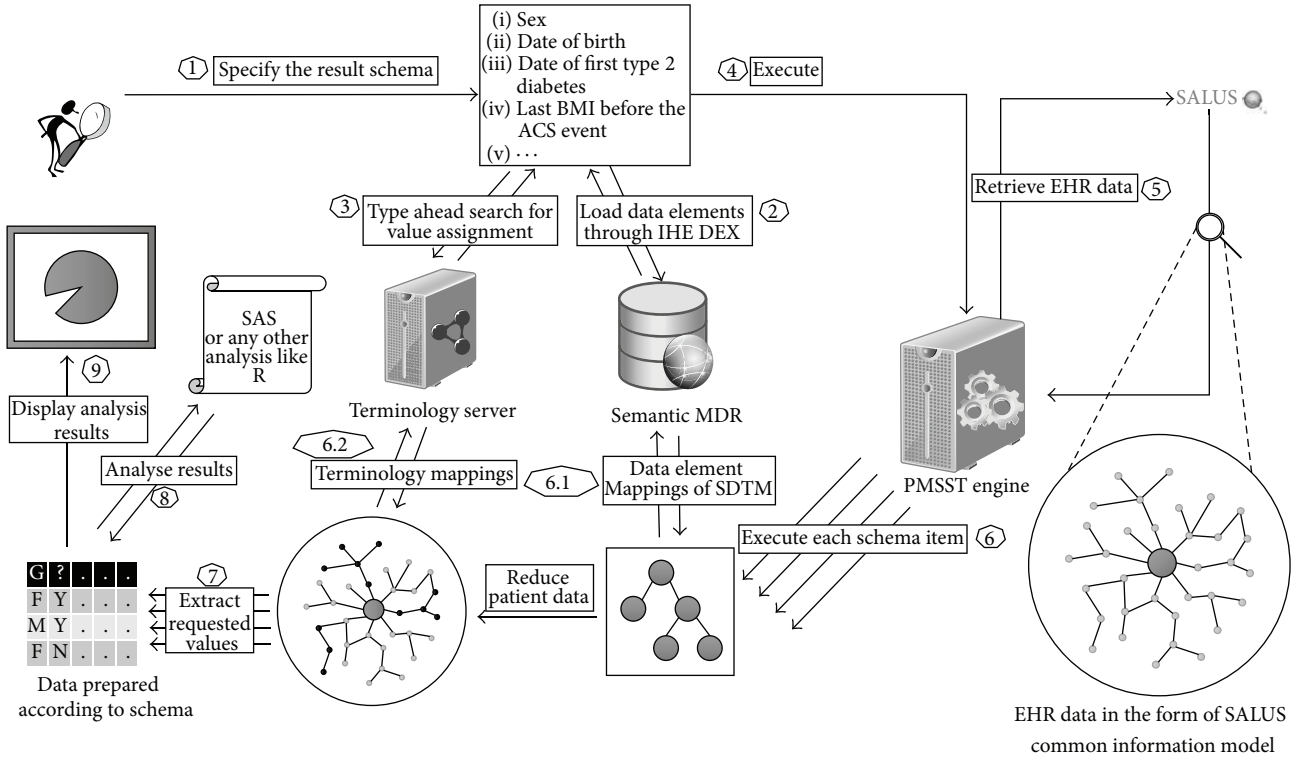

Figure 3: Step-by-step representation of the data flow between different components. A clinical researcher uses PMSST in order to define a data collection set schema so that when patient data is retrieved from the underlying EHR source(s), data will be automatically transformed to that schema.

for patient conditions while SDTM elements refer to MedDRA or NCI terms. The terminology server includes mappings between these different coding systems, and PMSST can do value matching with the help of this terminology server.

(7) As a result of these data extraction operations, the data collection set is populated conforming to the schema defined by the researcher.

(8) User can write analysis methods on top of this schema independently of the underlying EHR source model. In our deployment, Roche implements SAS scripts to do further analysis.

(9) Finally the analysis results are presented to the researcher.

2.3.2. How Semantic Interoperability Is Achieved through the Use of CDEs and a Semantic MDR. The CDE based data interoperability approach lets the PMSST interact with the semantic MDR through IHE DEX profile and retrieve abstract CDE definitions. The researcher interacting with the PMSST uses the data elements that she is used to in her research domain. The underlying architecture of the PMSST does not make any message translation between different content models (i.e., from SALUS CIM based patient summaries to SDTM conformant instances). Instead, the abstract CDE definitions and their semantic links maintained by the semantic MDR are processed in order to find an extraction specification to be executed on the content model to which the EHR data conforms. This clear distinction between the abstract and implementation dependent parts of the CDEs enables integrating the CDEs with the semantic web technologies and linked data principles by using the semantic MDR.

In our semantic MDR, the links between different sets of abstract CDE definitions can be established through well-known knowledge organization systems such as SKOS (i.e., skos:exactMatch) or any property can be indicated again with SKOS (i.e., skos:notation) or other ontological constructs.

PMSST makes use of the abstract CDE definitions of the SDTM variables retrieved from the semantic MDR. In order to enable the retrieval of the extraction specifications given the SDTM variables, we mapped the SDTM elements to the SALUS CDEs. We implemented an automatic content model importer on top of the open API of the semantic MDR for importing the SDTM variables and their mappings to SALUS CDEs. In this way, although the user defined the data collection set via SDTM variables, he becomes able to collect the requested data from the EHRs sources that can provide the EHR data of the eligible patients through SALUS common information model.

In the semantic MDR, SALUS CDEs have also mappings to HITSP C154 Data Dictionary [26] elements through skos:exactMatch semantic links. Semantic MDR is capable of processing these semantic links to establish the links

Table 2: Mappings of the common data elements: SDTM, SALUS CDE set, and HITSP C154 Data Dictionary.

SDTM	SALUS CDE	HITSP C154
DM	Patient	Personal Information
DM.DMSEX	Patient.Gender.CD	1.06 Personal Information Gender
MH	Patient.Condition.Condition	Conditions
MH.MHPTCD	Condition.ProblemCode.CD	7.04 Conditions Problem Code
MH.MHSTDTC	Condition.TimeInterval.IVLTS	7.01 Conditions Problem Date

between SDTM variables and HITSP C154 elements transitively. Table 2 lists some part of the mappings used during the execution of our implementation.

Although the usage of the tool starts with defining eligibility criteria and retrieving EHR data according to that query, our implementation is independent of the content model according to which the EHR data is shaped. For example, if the underlying EHR system can provide HL7/ASTM CCD based patient summaries, then PMSST can seamlessly process the data by using the corresponding extraction specifications retrieved from the semantic MDR. Because HITSP C154 defines XPath expressions from its CDE definitions to HL7/ASTM CCD based documents and PMSST can retrieve the extraction specifications through the HITSP C154 mappings, this time, the extraction specifications would be XPath expressions and clinical researcher would not be aware of this. This means that PMSST can automatically communicate with an EHR system which is capable of exporting HL7/ASTM CCD based document summaries and make the data available for clinical research automatically.

3. Results and Discussion

In the context of the SALUS project, PMSST and all related components have been implemented and deployed on top of the SALUS interoperability framework integrated with the central data warehouse of the Lombardy region, Italy. This regional database includes anonymized data of ~16 million patients with over 10-year longitudinal data on the average. Clinical researchers in Roche are validating the PMSST with real life use cases, one of which is presented in this paper. Till the actual deployment within SALUS, we worked with simulated data to collect further requirements from clinical researchers and improve the capabilities of PMSST.

For the eligibility criteria defined in the use case introduced in this paper, PMSST retrieved anonymized data of ~8000 acute coronary syndrome (ACS) patients from a population of ~16 million patients. The definition of the data collection set schema starts after retrieving the cohort based on the eligibility criteria. PMSST transforms the retrieved cohort data to the model defined by the data collection set schema. The eligibility query execution is not in scope of this paper.

The researchers in Roche cannot directly see the resultant data according to the privacy rules of the SALUS project. Instead, their analysis methods are executed on the returned dataset and the results of this execution are presented through the graphical user interface of PMSST. Researchers from Roche have implemented SAS scripts assuming that in the end they will have the data represented with SDTM variables, which they already use in their daily work. However, the data warehouse of the Lombardy region has a custom schema. SALUS technical and semantic interoperability solutions retrieve data from this custom database and transform to instances of SALUS common information model (CIM). The CDE based data interoperability approach has enabled the mappings between the SDTM variables and SALUS CDEs where the SALUS CDEs have their extraction specifications (SPARQL scripts in this case). With the help of this architecture, PMSST can extract data from the SALUS CIM based patient data by using the SDTM variables. Afterwards, the analysis routines (i.e., SAS scripts) of the clinical researchers run on the SDTM conformant data.

In order to assess the validity of the data collection set calculated by PMSST, we have conducted a comparative analysis. By issuing SQL queries to the data warehouse of the Lombardy region, we have obtained several statistics regarding the items in the data collection set and compared them with the set populated by PMSST. For instance, demographic analysis on Lombardy region data warehouse shows that 38.22% of ACS patients are females which is equal to the percentage of "Female" in "Sex" column of the resultant PMSST data collection set. Similarly, PMMST calculates the incidence "Patient died any time after start of ACS" as 34.63% which aligns with the real values calculated in LISPA data warehouse. These analyses over the items of the data collection set show that the dataset created by PMSST is correct compared to the original data and assure us about the reliability of the results.

One problem we observed during the analysis is that many items of data collection set defined in Roche use case were actually empty. For instance, there was no data in any of the patients regarding the systolic and diastolic blood pressure measurements, or history of smoking. To deduce the cause of the problem, we have investigated the LISPA data warehouse and found out that the available data is not fully structured. Those empty columns in the resultant data collection set were also missing in the data warehouse. This has hindered Roche researchers from full utilization of the PMSST according to the planned use case. On the other hand, the records which exist in the data warehouse, such as the ones related to congestive heart failure (CHF), have been processed by the tool accurately. Thus, we conclude that PMSST can be fully exploited once the underlying EHR source gets more structured and includes more data about the patients.

3.1. End-User Validation. In order to assess whether PMSST fulfills the intended use from an end-user point of view or not, it has been tested and evaluated by real end-users from Roche in the scope of the SALUS project. An evaluation and validation framework based on the ISO/IEC 25040 Software engineering, Software Product Quality Requirements and Evaluation (SQuaRE) standard has been developed. According to the developed framework, a total of 6 users including a data analyst and an epidemiologist have taken part in the evaluation in order to assess the feasibility of conducting a study over a particular EHR system by using PMSST.

We have built a PMSST specific questionnaire which is based on the Health IT Usability Evaluation Scale [35] and provided to the evaluators online. The results obtained from the questionnaire based evaluation can be summarized as follows:

(i) PMSST has been a positive addition to postmarketing safety studies.

(ii) Using PMSST makes it easier to define data fields (the Data Selection tab) to be extracted from the retrieved patient summaries.

(iii) Using PMSST enables defining data collection fields and performing data selection more quickly.

Apart from the questionnaire results, the evaluators provided specific comments addressing the benefits of PMSST in their studies. Currently Roche conducts safety analysis studies based on some sample EHR datasets it has. It has been concluded that having a tool like PMSST which enables extraction of selected data collection sets of a specified cohort selection from different EHR systems would be very beneficial for pharmaceutical companies as it will increase the size and variability of patient data pools. The data analyst and the epidemiologist from Roche positively agree on that PMSST has been successful to achieve its focused objective and the data provided by the tool is feasible and suitable for a wider range of observational clinical studies. On the other hand, they also report that the efficiency of the tool and the completeness of the data vary depending on the status of selected EHR data source.

3.2. Current Status and Availability of Software. The deployment in Lombardy region, Italy, can only serve the SALUS project partners (i.e., Roche) behind high security firewalls because of the privacy concerns. For the interested readers, we prepared a dataset of 50 simulated patients considering the real world facts that Roche has experienced from previous studies and ongoing work on Lombardy region database. A package of the deployable software including this simulated dataset can be requested from the corresponding author.

4. Conclusions

The PMSST, introduced in this paper, enables clinical researches to define data collection set schemas on which the postmarketing safety studies will be conducted without being concerned about the structure of the underlying data sources. The main benefit of utilization of CDE based interoperability architecture is the ability of developing surveillance methods which do not have to be restricted to the data model of the EHR source: cohort selection and data collection set definition can be easily done in researchers' own language (such as SDTM). Moreover, such an interoperability architecture allows the data collection operation to be run on distributed EHRs resources which might be using different content models to expose patient data.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Analysis of Requirements for the Medication Profile to Be Used in Clinical Research: Protocol Feasibility Studies and Patient Recruitment

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A "Medication Profile," the information about the medicines a person is using and has used, is a core part of many electronic health record systems and summaries. However, there is little objective research into the data elements that the profile should contain to support the uses it must serve. With the increasing emphasis on secondary uses of electronic health information, as well as supporting the requirements to support direct to patient care, the Medication Profile should also support the requirements from clinical research. However, there is little, if any, description of these available. This paper describes an analysis of a set of study eligibility criteria that was undertaken to investigate which medication-related data elements would be required to support two clinical research use cases: the parameters to query a patient's Medication Profile to assess their suitability for entry into a trial (patient recruitment) and the parameters to query a set of Medication Profiles in a data warehouse to assess whether the eligibility criteria as described would yield a reasonable cohort of patients as potential subjects (protocol feasibility). These medication-related data elements then become information requirements that a Medication Profile should ideally meet, in order to be able to support these two uses in the clinical research domain.

1. Introduction

As part of a larger requirements gathering exercise for the in-depth analysis of the content needed in an ideal Medication Profile from both direct to patient healthcare and clinical research, requirements from two of the processes in clinical research domain were studied. This paper focuses on the medication information requirements to support protocol feasibility and patient recruitment studies. Requirements from the other contexts will be published in due course, together with a larger set of recommendations.

The provision of accurate information about the medicines that a patient is using now and has used in the past is extremely important both for the provision of direct patient care and also for the so-called "secondary uses" of information for research. This information is often termed the patient's "Medication Profile"; however there is little if any consensus as to what a Medication Profile should contain [1–5].

Subjects are selected as suitable for recruitment into a clinical study based on eligibility criteria which are formally documented as part of the protocol for the study. Finding suitable subjects is known to be difficult [6, 7], and success in recruitment is variable [8]. Various strategies are being developed to support recruitment, including design and deployment of systems for protocol feasibility studies and subject identification and recruitment [9]. These use the content of prospective or actual eligibility criteria as queries against a patient data warehouse to retrieve either numbers of the likely to be eligible patients (for feasibility testing) or individual patients (for possible recruitment).

There has been little analysis of the content of eligibility criteria and none specifically on their medication-related content. van Spall et al. [10] undertook a systematic review of

the description of exclusion criteria (only) in published randomised controlled trials; 54.1% of the trials examined had "medication-related reasons" for exclusion meaning that over half of all trials studied required at least some medication-related information for eligibility assessment. Weng et al. conducted an examination of eligibility criteria specifically for their computability to support clinical research and focused on the semantic structuring of the criteria [11], rather than on their clinical content. Ross et al. [12] conducted an analysis to characterise eligibility criteria into three categories, one of which was "a treatment or intervention on the participant," which is presumed to include medication, and to quantify their patterns and the complexity of these patterns.

The aim of this work was therefore to analyse a set of study eligibility criteria and to specifically investigate in detail the medication-related data elements which could be used as parameters to query a patient's Medication Profile to assess their suitability for entry into a trial (patient recruitment) or to query a set of Medication Profiles in a data warehouse to assess whether the eligibility criteria as described would yield a reasonable cohort of patients as potential subjects (protocol feasibility). These medication-related data elements then become information requirements that a Medication Profile should ideally meet, in order to be able to support these two uses in the clinical research domain.

A subsidiary aim was to have some sense of the value, in terms of frequency of use, of each of these data elements, such that an assessment of their importance for the particular use case can be made: if a parameter is used in many eligibility criteria, the value of its presence in the Medication Profile is high and vice versa.

2. Method

The analysis studied eligibility criteria from 41 clinical studies conducted in Europe by nine different pharmaceutical companies provided to the EHR4CR project [13] specifically for use in protocol feasibility and patient recruitment studies. This set of 41 trials had been selected from the total of studies in progress at the EHR4CR Pilot Sites as being representative of clinical studies currently conducted in the domain; the selection was made by the EHR4CR EFPIA partners. There were 1112 individual eligibility criteria from these studies, although there was considerable variability in what each trial considered to be a single eligibility criterion. For some studies, a single criterion might contain a number of related parameters each of which must be satisfied, whereas in other studies each parameter was detailed as a separate criterion to be satisfied. Because the investigation was seeking a qualitative understanding of the requirements that eligibility criteria place on the Medication Profile compared to a truly quantitative measure, no attempt was made to normalise the pattern of eligibility criteria such that each described one and only one parameter; the eligibility criteria have been used and counted exactly as they were supplied by their authors.

Each of the eligibility criteria was examined and those whose parameter(s) involved medication information were identified for further detailed study, including categorisation. Medication Profile information has two main parts: the identification of the medication(s) themselves and information about their use in the patient, the dosage instructions; both of these aspects were examined in more detail to elicit requirements. Eligibility criteria describing adverse events to medication occurring during the study (i.e., after a subject has been recruited into the trial) were not included for detailed evaluation (e.g., "any other hemorrhage/bleeding event > CTCAE Grade 3 within 4 weeks of first dose of study drug"). However, eligibility criteria that described adverse events to medication that had occurred prior to the study and which therefore might be expected to be documented in a patient's Medication Profile were identified and evaluated.

To provide some comparison to the medication information based data elements, eligibility criteria whose data element(s) involved laboratory test information were also identified. Laboratory test information was defined as biochemistry and haematology tests only; observables such as blood pressure measurement, pathology, and microbiology information were not included. Laboratory test information was chosen as a comparator for medication information as like medication information, it is highly structured with little additional free text and is similarly stored in patient records.

3. Results

Of the 1112 eligibility criteria, there were 201 that made a direct reference to medication that a potential subject may be taking or may have taken.

In addition, there were 79 eligibility criteria that described medication-related information (allergy to medication and adverse events from medication administration) that should be available from an extended Medication Profile or that could be queried by inference.

The number of eligibility criteria that involved laboratory test information was 99; 39 were inclusion criteria and 60 were exclusion criteria.

4. Categorisation

The 201 eligibility criteria containing reference to medication-related data elements were examined in detail and categorised on the basis of whether they referred to current or past medication use and whether they referred to medication information use in context of a diagnosis, to use of medication that was a study agent in a previous study, or to a medication failure (Figure 1).

"*Current medication use*" is defined as those eligibility criteria that identify a medication (or group of medications which might be defined by therapeutic category or by shared indication) being taken by a patient/potential subject at the time of recruitment into a study using words and were identified by phrases such as "(current) use of" or "concomitant administration of." The large majority of these were exclusion criteria with just 2 being inclusion criteria.

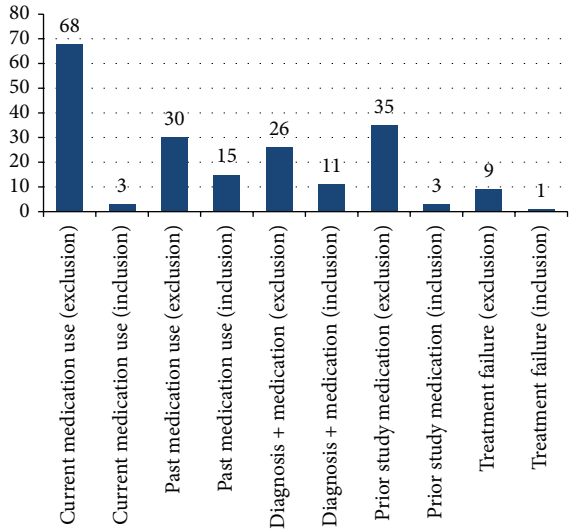

Figure 1: Graph showing the initial categorisation of medication-based eligibility criteria.

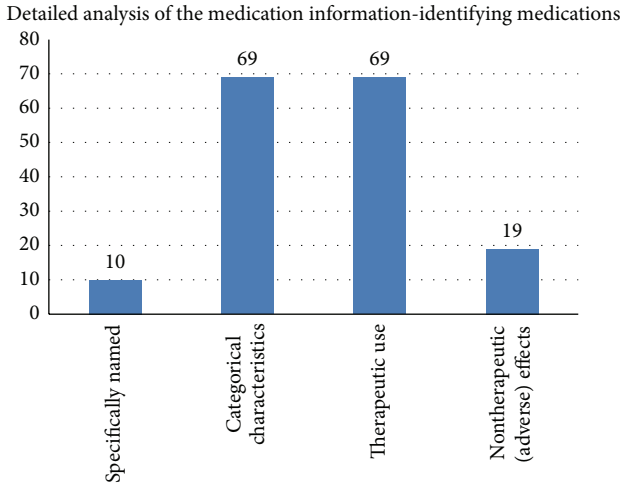

Figure 2: Graph of the various ways to identify medications in eligibility criteria.

Example:

"*Currently on any medication to treat high blood pressure.*"

Included in the "current medication use" category are those eligibility criteria where there was some indication of the timing of the medication administration in relation to the current point in time or to a particular point in the study such as randomisation, for which it is likely that the medication would (still) be used "in the present."

Example:

"*Treatment with oral neuroleptics within 4 weeks prior to the screening visit.*"

"*Past medication use*" is the category of eligibility criteria that describe a medication (or group of medications) that has been taken in the past and is no longer being taken (words and phrases such as "prior administration or" or "history of"). Some eligibility criteria were not explicit in their reference to past medication use, for example, the criterion "at least one but not more than 2 cytotoxic chemotherapy regimens for metastatic castration-resistant prostate cancer"; this implies that the chemotherapy must have happened previously to "now" and would therefore be recorded as "past." The "past medication use" criteria were split with two-thirds being exclusion criteria and one-third being inclusion criteria.

Example:

"*History of prior exposure to carisbamate.*"

The set of eligibility criteria described as "*Diagnosis + Medication*" are those where the primary criterion is that the subject has the condition/symptom described (a "diagnosis") with a supplementary qualification identifying a medication. The subject must have both the condition and symptom (diagnosis) and be using or have used the treating medication to fulfil the criterion.

Example:

"*Cardiac arrhythmias requiring anti-arrhythmic therapy.*"

"*Prior study medication*" is the category of eligibility criteria which describe the use by a patient of a study agent in a previous study; the overwhelming majority (35) was exclusion criteria, but there were 3 that were inclusion criteria (such that the patient would be eligible as a subject for a "follow-on trial").

Example:

"*Investigational drug therapy outside of this trial during or within 4 weeks of study entry.*"

There were 10 eligibility criteria that concerned "*treatment failure*" which was recognised by phrases such as "inadequate response to," "resistance/resistant to," and "relapse after"; with just one exception these were all inclusion criteria (Figure 2).

Example:

"*History of inadequate response to at least 1 AED* . . . ."(where AED = anti-epileptic drug).

Only 10 of the 201 eligibility criteria named a specific medication; all the others used a class description referring to characteristics or use of the medicines in that class.

Medications were described on the basis of their *categorical characteristics*, for example whether they are in the chemical group of "bisphosphonates" or "anthracyclines" or share a common mechanism of action, for example "beta-blockers" or "glucocorticosteroids." These grouping features are part of the categorical information about medicines; information is always and necessarily true for that medicine.

Example:

"*Chronic treatment with a non-steroidal anti-inflammatory drug.*"

Medications were also described and identified as a group on the basis of their *therapeutic use,* for example, whether they

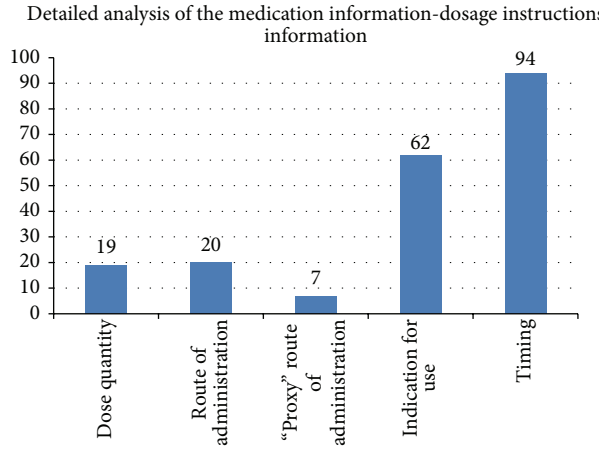

Figure 3: Graph of the types of dosage information in eligibility criteria.

are used to treat hypertension or in cancer chemotherapy. This information is not part of categorical medicinal product information, it is contextual, and it changes over time. For example, for many years aspirin (acetylsalicylic acid) was used only as an analgesic and antipyretic and then it was discovered to have antithrombotic properties and so is now additionally used as secondary prevention therapy after myocardial infarction, stroke, and a variety of other cardiovascular events, so its therapeutic use has changed over time.

Example:

> "*Patients receiving antipsychotics who are not on stable doses of atypical antipsychotics for four weeks prior to baseline.*"

Just as medications can be described and identified as a group according to their therapeutic use, they can also be grouped by particularly *significant nontherapeutic effects*; these are usually considered to be unwanted and undesirable and are therefore often known as "adverse effects." This information is also contextual and changes over time, especially as experience with the use of the medications grows.

Example:

> "*Any concomitant medication known to prolong the QT interval.*"

Medications in eligibility criteria were described and identified as a group by their *authorisation status*, whether or not they have a formal marketing authorisation. This information is factual information about medicinal products at a point in time within their overall development lifecycle (Figure 3).

Example:

> "*Treatment with a non-approved or investigational drug within 30 days before Day 1 of study treatment.*"

Dosage instructions information [14] is information about dose quantity (individual dose quantity, daily dose quantity, or cumulative ("lifetime") dose quantity), about timing of administration (frequency of individual administrations or duration of the course of therapy or start/stop dates) and about route of administration. Indication information is not considered a core component of the dosage instructions information but is assessed with them as provision of the reason for the medication can be given as part of the instructions.

Less than 10% of the medication focused eligibility criteria made any reference to *dose quantity information* and of those half of those criteria did not specify a dose quantity per se but specified "stable dosage" or "changing dosage" as part of their description, implying that dose quantity would need to be queried.

Example:

> "*Low dose warfarin (1 mg po qd) is permitted if the INR (international normalized ratio) is <1.5. Low dose aspirin is permitted (≤100 mg daily).*"

A similarly small percentage of the eligibility criteria specifically referenced one or more *routes of administration* for medications directly (oral and intravenous) and further 7 criteria referenced route of administration by the proxy grouper concept of "systemic," which implies oral or parenteral routes of administration (as opposed to topical routes).

Example:

> "*Patients that required any use of IV vasodilators.*"

However more than a quarter of all medication focused eligibility criteria described the *indication* for use of the medication as part of their content.

Example:

> "Patients in whom anticoagulant treatment for their index PE or DVT should be continued."

Almost half of medication-based eligibility criteria described some element of the *timing of the medication administration*. Of these, 73 were "within" and 11 were "prior to" a certain point, usually a milestone in the study lifecycle, screening, randomisation, or first dose of study medication. The others were "for at least. . .before."

Interestingly, some eligibility criteria, and particularly those describing use of another investigational agent, also stated a time period in terms of "within x days or 5 half-lives, whichever is longer."

Example:

> "*History of felbamate treatment within the past 3 months.*"

5. Other Types of Medication-Related Information

The 79 eligibility criteria that referenced medication-related information that could possibly be included in a broad Medication Profile were categorised as described in Figure 4.

All the eligibility criteria that described *allergy or hypersensitivity* to a medication or an excipient were exclusion criteria.

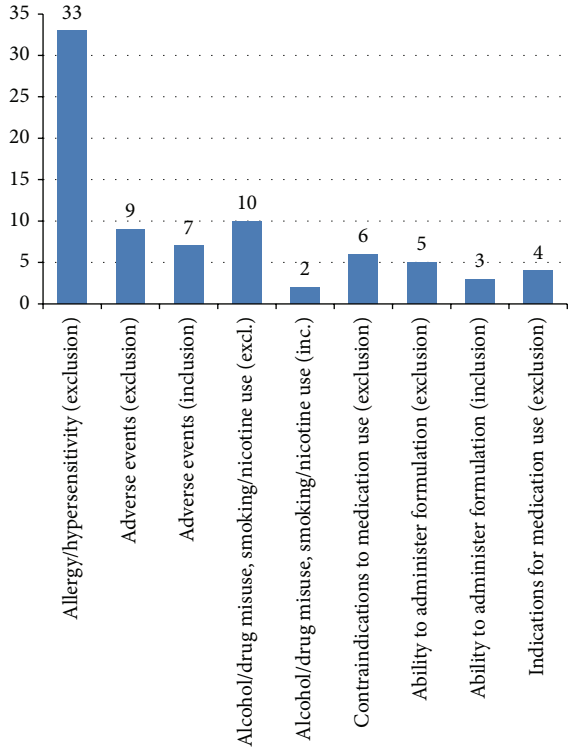

Figure 4: Graph of the types of medication-related eligibility criteria.

Example:

> "*History of hypersensitivity to docetaxel or polysorbate 80.*"

Eligibility criteria describing *adverse events* to a medication or type of medication were mostly exclusion criteria. Note that an allergy could be considered an adverse event and also included in this category but in this analysis was classified separately if specifically described (as above).

Example:

> "*Unresolved or unstable serious adverse events from prior adjuvant chemotherapy or radiotherapy.*"

There were 12 eligibility criteria looking at current or past *substance and alcohol misuse*, either directly or by referencing screening and/or current or past smoking status and nicotine use. Two criteria were listed as inclusion criteria, but they specified a "negative result" which semantically means that they were effectively exclusion criteria.

Example:

> "*Current alcohol dependence or drug abuse.*"

All the eligibility criteria which were described in terms of *contraindications* to a medication or group of medications were exclusion criteria.

Example:

> "*Contraindications to the use of corticosteroid treatment.*"

Some eligibility criteria described the *subject's ability or otherwise to administer*/have administered the medication in a particular formulation.

Example:

> "*Patients unable to swallow oral medications.*"

All the eligibility criteria which described the subject being *indicated for treatment* with a medication or group of medications were exclusion criteria; in these criteria the indication for medication use is used as a proxy for a set of diagnoses.

Example:

> "*Indication for anticoagulant therapy for a* condition other than atrial fibrillation (e.g., VTE)" (where VTE is venous thromboembolism).

6. Discussion

6.1. Importance of Medication Profile Information. The results of the analysis show that just over 18% of the 1112 examined eligibility criteria from the 41 clinical trials made reference to medication information. This information therefore needs to be present in a potential subject's Medication Profile in order to ascertain whether that person would be eligible for a study. This proportion is approximately double the proportion of examined eligibility criteria that referred to laboratory test information, which provides good evidence of the value of using a patient's Medication Profile for protocol feasibility studies and in the development of computer platforms and tools to support patient recruitment.

This proportion is considerably lower than an analysis conducted by Ross et al. [15], which found, of 1000 eligibility criteria studied, "criteria specifying treatments or interventions participant has received or will receive" accounted for 34% of the total; however no clear definition of the difference between a "treatment" and an "intervention" is provided in that analysis. The proportion of eligibility criteria referencing laboratory data was also lower in the Ross analysis, 9% as opposed to 23%; this suggests that the categorisation in this analysis was more granular than that of Ross et al.

6.2. Current Medication and Past Medication. The analysis shows the relatively high level of importance of a subject's current medication as compared to the medication history, in that almost twice as many eligibility criteria referred to medication administered "now" (and including prior to and including "now") as referred to those having been administered in the past and are no longer being administered. Note that in the context of eligibility criteria the "now" may well be a specified point in the trial process, randomisation, first administration of the investigational product, and so forth. However, if the number of eligibility criteria that focus on previous administration of a study agent, which is a type of "past medication," is included, this would give roughly equal value to knowledge of "current" and "past" medication. This is important because in the healthcare delivery domain the current medication is deemed to be the more important, for decision support, and so forth, with a longitudinal record being of lesser importance.

6.3. Investigational Product Use. There are a significant number of eligibility criteria that refer to previous administration of a study agent or to the authorisation status of products that have been previously administered, which includes use of an authorised medication outside of its approved indications.

This is significant because in recent years there has been a growth in the use of study registries which, accompanied by the concentration of clinical research in a smaller number of large centres, means that the reuse of potential subjects is becoming a problem.

In order to correctly interrogate a Medication Profile for use of study agents or other nonapproved drugs, it has to be possible to identify these. There are two possibilities. One is to incorporate the use of a medicines knowledge base that has wide coverage of study agents as part of the query application (see below) that could be used to compare all the medicines in a patient's profile with their authorisation status in the country of use. Unfortunately, most medicines knowledge bases do not have full coverage of investigational agents because information about these is not widely available and putting such information, even in a limited way, has sometimes been deemed "advertising," which is not permitted for unauthorised medicines. Even though there is a move from the regulatory agencies to increase the availability of information on investigational products and an acceptance that inclusion of basic information about an unlicensed product in a knowledge base is not "advertising," it is likely to be some several years before such information is widely available and is useable in a computable way. Even if the information was available, the comparison of each and every medicine in a profile against an authorisation status is a considerable task, especially for protocol feasibility testing when a large volume of potential patients' information is being queried. The second possibility, therefore, is to indicate directly into the Medication Profile when a patient is taking an investigational agent. This is not, to the writer's understanding, currently done in any formal way by any medication recording system (PMR or EHR) used in direct patient care but on the evidence of this analysis would appear to be useful.

6.4. Identifying Medicines—Knowledge Base Requirement. Only a very small number, less than 3%, of eligibility criteria that focus on the subject's use of medicines directly describe the medicines themselves; all the rest describe medicines in groups, either by categorical characteristics or by therapeutic use, or indeed by nontherapeutic effect.

This is significant for any process that wishes to use Medication Profile information in protocol feasibility studies and/or in tooling to support patient recruitment in that it introduces a requirement for knowledge about medicines to be available for use. A medicines knowledge base, such as those produced to support medication decision support in direct to patient care, should have the categorical information and the therapeutic use information readily available and in a format that would be straightforward to process to provide the additional information to support the querying of these eligibility criteria [16]. A knowledge base of this type will use the Summary of Product Characteristics (SmPC) as one of its primary sources. In that document, which is laid out in standard sections [17], the categorical characteristics of a medicine are described in the "pharmacodynamic properties" section (section 5.1 of an SmPC) usually a direct reference to a formal characteristics classification such as the ATC [18]. Therapeutic use is similarly described in the "therapeutic indications" section (section 4.1 of an SmPC).

However, although nontherapeutic effect information of the types seen in the eligibility criteria is available for medicinal products as part of this authorisation information, it is not as organised and as accessible as the categorical characteristics or indications information nor is it standardised. For although there is a section in an SmPC labelled "undesirable effects" (section 4.8 of an SmPC) this merely lists all unwanted effects that the medication has been found to cause or suspected of causing. For newer medicines these effects are at least grouped together in categories based on the MedDRA "System Organ Class" [19] hierarchy and therefore it is possible to more easily identify those of relevance to an eligibility criteria, say, by looking at the cardiac disorders for QT interval prolongation. But this type of adverse effect information may also or alternatively be described elsewhere, as in the "special warnings and precautions for use" [20] section (section 4.4 of an SmPC).

Information about enzyme modulation caused by a medicinal product may be even more dispersed in a single SmPC. It may appear in the "posology and method of administration" section (section 4.2 of an SmPC) because it is seen as a requirement for dosage adjustment; or it may appear in the "special warnings and precautions for use" part (section 4.4 of an SmPC) as information about coadministration and it will almost certainly also appear (again) in the "interaction with other medicinal products and other forms of interaction" (section 4.5 of an SmPC). Therefore, although the raw data is usually available, even if somewhat scattered in location, this has not be processed into useful knowledge for use in practice. For example, there is no well documented and agreed set of medicines acknowledged as those which prolong the QT interval in a clinically relevant manner. An illustration of this is that the British National Formulary lists QT interval prolongation as side effect of macrolide antibiotics [21] but does not do so for quinolone antibiotics although such effects have been documented [22] and indeed are noted in SmPC [20]. The same is true for cytochrome P450 isoenzyme modulators and indeed is more complicated as there are several individual isoenzymes to consider. Knowledge bases currently take this raw data on enzyme modulation and apply it in the maintenance of their drug interaction applications, rather than provide it directly as information about the medicinal products that are CYP modulators [23]. Recognising this issue, some clinical trial protocols will document lists of medications that in their context are considered to carry these risks, for example, "any concomitant medications that may cause QTc prolongation or induce Torsades de Pointes (see the Appendix for the list of medications in Tables 1 and 2) or induce CYP3A4 function" and "concomitant use of CYP3A4 inhiibitors or inducers. See Section 5.3.2 for list of prohibited medications." But these are not standard lists and have to be managed on a study by study

Table 1: Results summary: eligibility criteria containing medication information.

Eligibility criteria making direct reference to medication information	201 (18.1%)	178 exclusion 33 inclusion
Current medication use	71 (35.3%)	68 exclusion 3 inclusion
Prior study medication	45 (22.4%)	30 exclusion 15 inclusion
Diagnosis with medication use qualifier	37 (18.4%)	26 exclusion 11 inclusion
Other study participation	38 (18.9%)	35 exclusion 3 inclusion
Treatment failure	10 (5.0%)	9 exclusion 1 inclusion

Table 2: Results summary: identifying medicines in the medication information in eligibility criteria.

Medicines specifically named	10 (5.0%)
Identified by categorical characteristics (e.g., chemical group)	69 (34.3%)
Identified by therapeutic use	69 (34.3%)
Identified by nontherapeutic effects (e.g., adverse events caused)	34 (16.9%)
Identified by authorisation status	19 (9.5%)

basis and cannot necessarily be applied to other studies that have not provided such information.

There were a small number of eligibility criteria that described alcohol and/or substance misuse and/or nicotine use. Whilst not directly part of the Medication Profile, there is information that could contribute to this. Medications used specifically in the management of substance misuse, alcohol misuse, and nicotine replacement therapy are likely to be documented in a profile and, by using a knowledge base to identify these and then querying against that set, some assessment of a potential subject's suitability against this type of eligibility criteria could be made using information in the Medication Profile.

A knowledge base could be used to provide information to assist in querying for the small number of eligibility criteria that reference contraindications to medications, by listing these contraindications as conditions and then the patient record querying for evidence of their presence directly. However, this is a considerable amount of processing for a relatively small number of eligibility criteria; it would be more constructive to protocol feasibility studies and patient recruitment support to list the conditions themselves, rather than use a medication's contraindications as a proxy.

6.5. Dosage Instructions. The proportion of eligibility criteria that describe use of medicines and that also referenced dosage instruction information showed some clear patterns. Less than 10% described either dose quantity, frequency of administration, or duration of the course of therapy, and a similar proportion described route of administration. However, nearly half of all eligibility criteria that describe use of medicines also reference when the course of therapy occurred, either that it was currently in progress or how long in the past it had occurred and ceased, as already described in the classification of those eligibility criteria that reference either current medication or past medication.

Given the complexity that can easily develop in describing dosage instructions information in a machine readable way, these results indicate that there is little value to be obtained by attempting complex querying of this information within the Medication Profile for protocol feasibility studies and patient recruitment tooling. But the results show that it is important for protocol feasibility studies and patient recruitment tooling to be able to ascertain the basic timing of the course of therapy (i.e., start and stop dates), even if the detail of the dose quantity, frequency of administration, or route of administration within that course is not provided in any machine readable/queryable way.

6.6. Indication for Treatment and "Reason to Stop". 30% of eligibility criteria that include medicinal product use also require evaluation of the indication for the use of the medication, but this information is rarely directly recorded in a Medication Profile and therefore is presently unlikely to be directly available in a clinical data warehouse or EHR system.

The information may well be present implicitly; the patient was diagnosed with breast cancer at point X and three weeks later doxorubicin is administered; it is almost certain that the doxorubicin would be indicated for the treatment of the breast cancer. So whilst a clinician reviewing a patient with a complete health record can make that connection straightforwardly, an application querying a clinical data warehouse or EHR system would find that an extremely complex task to accomplish successfully given the current state of such systems. And even a clinician may find this type of inference difficult for those medications with a diverse set of therapeutic uses; being clear of the indication for the use of amitriptyline, whose primary use has been as an antidepressant but is now as likely to be used as an analgesic in postherpetic neuralgia or as a prophylactic against migraine, is a much more tricky task.

Note that indication information in an eligibility criterion is subtly different from the combination of a particular diagnosis with a medication qualifier, although each describes a medication and a condition/symptom being treated. The latter is somewhat easier to query for in a clinical data warehouse or EHR system; the diagnosis can be queried directly, and if found, then the qualifying medication can be investigated, again directly. Since both mechanisms achieve roughly the same ends, potential subjects with a particular diagnosis also taking a particular medication that is related to that diagnosis, wording eligibility criteria in the pattern of "diagnosis + medication qualifier" is likely to be more efficient for querying in protocol feasibility studies and patient recruitment tooling than using the "medication and indication" pattern.

A small number of eligibility criteria referred directly to treatment failure; the subject had therapy with the particular

medication, but it was unsuccessful. In addition, in the analysis of those criteria which were deemed as not being directly related to the Medication Profile but referenced medication in some way, the majority concerned allergy/hypersensitivity or an adverse event. If these are considered together as "reason(s) to stop" a therapy, this amounts to significant number of the eligibility criteria. "Reason to stop" information is rarely recorded directly, but these results suggest that it would be of use if it were.

Currently, there is nothing formally available that would provide information to support a query for the very small number of eligibility criteria that are concerning a potential subject's ability to self-administer particular formulations of a study agent. This type of information is more likely to be recorded in nursing and care notes than in any other part of a patient's health record.

6.7. Ethical and Medicolegal Implications. This analysis of eligibility criteria requirements for the Medication Profile has focused on the medication specific data elements that the profile would need to contain in order to support the systems mediated detection of suitable subjects for protocol feasibility testing and patient recruitment. However, in order for these data to be actually used in such testing or going forward as part of a clinical trial data set, it would be necessary to comply with all the appropriate ethical and medicolegal requirements, including those of Good Clinical Practice (GCP) [24]. These include the requirement that the authorship and time stamping of all data are preserved and that all changes are made in a version controlled manner permitting full traceability and the potential for rollback to a prior version of the data, a comprehensive audit trail and a long-term commitment to data retention. Many of these GCP medicolegal requirements are identical or very similar to the medicolegal requirements for electronic health record data, such as those published in ISO 18308:2011 "Requirements for an electronic health record architecture" [25].

7. Conclusion and Recommendations

Information from a potential subject's Medication Profile makes a significant contribution to the overall set of queries, based on study eligibility criteria, which are used in protocol feasibility studies and patient recruitment tooling.

Information on both current medication use and past medication use was shown to be equally useful, when use of a past study agent is included as a type of past medication, which supports the requirement to have longitudinal information in a Medication Profile as well as current medication information.

In terms of the detail of what is recorded in the profile in addition to the identification of the medicinal products themselves, the most useful element is the timing of the course of therapy, when it commenced and if/when it has ceased. Other dosage information, including route of administration and dose quantity, was found to have limited use. In conjunction with the start and stop timing, direct recording of information about the indication to start a therapy and reasons for its cessation were found to be of benefit in this context. Neither is currently recorded in routine practice.

The analysis demonstrated the requirement to be able to query a Medication Profile to ascertain whether any of the medications that a patient has received is an "investigational agent" (i.e., a medication which does not possess a marketing authorisation and therefore is administered as part of formal clinical research).

It was clear that, due to the way eligibility criteria are currently written, a medicines knowledge base is required to expand some grouping concepts from the criteria into individual medication concepts such that the Medication Profile can be queried directly. In addition, it is recommended that further work be undertaken in this context to produce standard and agreed sets of medications acknowledged to cause particular nontherapeutic effects that are known to be of concern in clinical trials, most particularly those medicinal products that prolong the QT interval and those that cause CYP modulation. This would have value in the wider context of clinical decision support as well as for study design and execution.

It was interesting to note the similarities and differences between two particular patterns of eligibility criteria, the "diagnosis + medication qualifier" pattern and the "medication + indication" pattern. Given the known lack of recording of indication information, the former pattern appears to be the more useful; yet the latter pattern appears to have more extensive use in eligibility criteria. Further investigation in this area could be undertaken to further explore the similarities and differences, and if there was evidence that the one pattern was significantly more effective in protocol feasibility studies and patient recruitment tooling, this should be reflected back to those working in study design. It should be noted that optimisation of the eligibility criteria given in a study protocol would be expected to optimise recruitment of subjects to that study, so this would indeed be a useful area for further work.

This study examined just over a thousand eligibility criteria from 41 phase III studies into new medications; a similar type of investigation could be conducted on other study phases and study types. This should include observational (phase IV) studies for medications and studies into other types of medical intervention (procedures and device use) to confirm if similar patterns of information requirements exist or indeed whether these types of studies place additional requirements for information on the Medication Profile.

The results of this analysis give several recommendations, beyond the provision of requirements for the content of a Medication Profile. These recommendations are primarily aimed at authors of eligibility criteria but also to authors of medicines knowledge bases and to the providers of electronic health record systems. Medication Profile information in EHR systems should be structured and designed such that their recording of medication information and in particular the granularity of the data elements within that support all of the relevant use cases for that information: high quality direct care delivery and also secondary uses, including clinical research.

Table 3: Results summary: identifying dosage instructions information in eligibility criteria.

Dose quantity	19 (9.5%)
Route of administration or "proxy"	27 (13.4%)
Indication for use	62 (30.8%)
Timing information	94 (46.8%)

If an eligibility criterion needs to identify subjects using a medication to treat a particular condition, rather than stating the medication and indication (medicine X to treat condition Y), based on this analysis it is more useful to state a "diagnosis Y and treatment with X," as a diagnosis and a medication are much more likely to be separately present and queryable in a health record than the medication with its indication for use.

Standardised sets of the medications that are acknowledged to cause important clinical effects such as prolongation of the QT interval and CYP modulation should be developed. These should be agreed for use in both direct to patient healthcare and clinical research and should be available for use in knowledge base systems.

In the interim, when an eligibility criterion refers to such an effect, it should provide the set of medications that the author deems to be causative, to avoid different investigators using different sets.

These conclusions and recommendations will be combined with other recommendations and requirements from the analysis of other uses and processes for patient medication information and will be used to develop the specification for a cohesive and comprehensive Medication Profile which will be published later.

Appendix

Results Summary Tables

See Tables 1, 2, and 3.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Using Electronic Health Records to Support Clinical Trials: A Report on Stakeholder Engagement for EHR4CR

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Background. The conduct of clinical trials is increasingly challenging due to greater complexity and governance requirements as well as difficulties with recruitment and retention. Electronic Health Records for Clinical Research (EHR4CR) aims at improving the conduct of trials by using existing routinely collected data, but little is known about stakeholder views on data availability, information governance, and acceptable working practices. *Methods*. Senior figures in healthcare organisations across Europe were provided with a description of the project and structured interviews were subsequently conducted to elicit their views. *Results*. 37 structured interviewees in Germany, UK, Switzerland, and France indicated strong support for the proposed EHR4CR platform. All interviewees reported that using the platform for assessing feasibility would enhance the conduct of clinical trials and the majority also felt it would reduce workloads. Interviewees felt the platform could enhance trial recruitment and adverse event reporting but also felt it could raise either ethical or information governance concerns in their country. *Conclusions*. There was clear support for EHR4CR and a belief that it could reduce workloads and improve the conduct and quality of trials. However data security, privacy, and information governance issues would need to be carefully managed in the development of the platform.

1. Background

Electronic Health Records for Clinical Research (EHR4CR) is a large private-public partnership project which involves 34 academic and private partners, including 11 academic health provider sites across France, Germany, Poland, Switzerland, and the United Kingdom [1]. The project aims to design and build a robust and scalable platform to reuse data from Electronic Health Record (EHR) systems whilst adhering to ethical, regulatory, and data governance policies within each of the countries of the participating sites.

The aim of the EHR4CR platform is to support the conduct of clinical trials, specifically to (1) assist in the assessment of trial feasibility, (2) aid patient recruitment, (3) allow automated preloading of clinical information from a patient's EHR to a trial data collection form, and (4) use EHR information in the reporting of Serious Adverse Events (SAE) during a trial.

There are increasing challenges in the clinical trials environment from economic pressures and regulatory demands. The pharmaceutical industry in particular is investing more in clinical research, year-on-year, but bringing fewer new drugs to the market. Around 57% of pharma research costs are spent on the conduct of clinical trials [2], and yet this stage of drug development contains significant avoidable costs, such as protocol amendments due to recruitment delays [3] (costing around $0.5 million per amendment). However, there is also a growing consensus that the use of EHRs

can provide new and unique opportunities to develop more efficient trial processes. Previous work has shown that use of EHRs can improve quality assessment, epidemiological research, and clinical trials within primary care [4], and using EHRs can improve patient recruitment rates to trials [4–6]. However there are still few examples of where research data are integrated with patient clinical data [7] and there are concerns around meeting privacy, regulatory, and data governance requirements when using EHRs for research [8, 9].

To better understand how different technical approaches would be seen in terms of ethical, regulatory, and data governance attitudes across the different countries we decided to conduct a series of structured interviews with senior figures in healthcare organisations across Europe (including managers and information governance staff, academics, clinical opinion leaders, ethicists, and research funders).

2. Methods

Materials for the conduct of structured interviews with senior figures in healthcare organisations across Europe (including managers and information governance staff, academics, clinical opinion leaders, ethicists, and research funders) were developed based on detailed interviews conducted in a pilot study in Glasgow, Scotland [10]. The final interview schedule consisted of a series of questions relating to different aspects of the project which the interviewee responded by using a five-point Likert scale (Strongly Agree/Agree/Neither/Disagree/Strongly Disagree) and a number of free text responses for other issues not raised within the set questions.

The principal investigator at each of the pilot sites participating in EHR4CR was contacted and asked to conduct interviews for the stakeholder engagement survey with key people in their own geographic area using a snowball sampling technique [11]. The selection of participants was left to the discretion of each site so they could best utilise their local knowledge and networks, although different categories of interviewee were defined. Potential interviewees were contacted and asked to participate and if they agreed a time was set either for a face-to-face or telephone interview, dependent on the interviewees' preferences. The interviews were conducted by senior members of project staff (usually the PI) in the second half of 2012 and the first half of 2013.

The interviewees were provided with a description of the project and structured interviews were conducted initially focusing on the four project objectives (trial feasibility, facilitating recruitment, facilitating clinical trial delivery, and reporting of adverse drug events). Within each objective a series of scenarios as illustrated below were presented and related questions posed.

3. Trial Feasibility

Access to patient data is required to inform trial design and trial feasibility assessment and so information and governance approval would be required for the generic process rather than a specific trial. A clinical research sponsor would be interested in examining the prevalence or incidence of a disease or the rate of clinical outcomes of interest. By comparing a defined set of inclusion/exclusion criteria against data held at a number of centres this would help improve trial design, in particular by estimating the likely number of patients who would match the eligibility criteria, thereby allowing a more accurate prediction of recruitment rates per site.

The first part of the interview questionnaire presented four different options, as Scenarios A–D, for the kind of information that could be extracted from a hospital EHR system and returned to the research sponsor.

Scenario A. Only the total number or percentage of eligible patients meeting all criteria is returned to the research sponsor.

Scenario B. The total number or percentage of eligible patients meeting each individual criterion is returned to the research sponsor.

Scenario C. Total number or percentage of eligible patients meeting each criterion is returned to a third party to work on behalf of the research sponsor.

Scenario D. Deidentified individual patient records relating to the eligibility criteria are returned to the research sponsor.

A set of questions were posed regarding the acceptability of each of the four scenarios, from different ethical and governance perspectives.

4. Facilitating Recruitment

Once a clinical trial protocol has been finalised, the EHR4CR platform could transmit the patient eligibility criteria electronically to each participating hospital or another participating organisation, for example, community mental health team. This part of the interview questionnaire explored the acceptability of using these electronic criteria to support a hospital to identify and contact potentially eligible patients (Scenario E).

Scenario E. Routinely collected patient data could be used to facilitate the identification of potentially eligible recruits for the trial at a centre, given that all relevant permissions are in place. The study inclusion/exclusion criteria would be provided and run on behalf of the investigator against the local database to extract a list of potentially eligible patients. The local investigator could select individuals from the list as appropriate and generate letters of invitation to participate in the trial to the patients. No individual patient level data would be returned to the organisation conducting the clinical research prior to patient consent.

5. Facilitating Clinical Trial Execution

The next two scenarios related to information on patients who have been recruited into the trial and provided full informed consent for the use of their electronic health record.

Scenario F. Data is extracted from the electronic health record into the trial database to facilitate trial conduct. There would be an option to allow the investigator to approve each data transfer.

Scenario G. Data collected specifically for the trial is added to the patient's electronic health record.

Interviewees were asked to comment on the acceptability of each of these two scenarios, which are not mutually exclusive.

6. Reporting of Adverse Drug Events

The final four scenarios focused on the electronic extraction and communication of data about a serious adverse event occurring during a clinical trial. These scenarios portrayed different aggregation levels of patient data.

Scenario H. Individual patient records relating to adverse event data and associated clinical and prescribing data are returned to the organisation conducting the clinical research.

Scenario I. Individual patient records relating to adverse event data and associated clinical and prescribing data are returned to a local clinician to support the completion and submission of each ADE to the marketing authority and the regulatory agency, as appropriate.

Scenario J. Automated extraction of periodic aggregated summary information on adverse events extracted from electronic records and reported to the marketing authority and the regulatory agency, as appropriate.

A final scenario (Scenario K) describing the use of an existing national dataset of deidentified patient data was described and interviewee responses to related questions were collected.

7. Motivations and Threats

In addition, a series of questions were posed relating to (a) motivating factors for a hospital/academic institution to participate in trials using the proposed EHR4CR platform and (b) threats and challenges to the success of an EHR4CR platform to support trials. Finally, interviewees were asked to give their overall impression of the EHR4CR project.

Responses from each interviewee were recorded using a standardised form relating to the specific questions asked within the interview. These were then anonymised and returned to the Robertson Centre for Biostatistics, University of Glasgow, where they were entered into a study database. The individual identities of each interviewee were not recorded. Each interviewee could be categorised by country and their job role, although some may have had multiple roles (e.g., clinical and academic). Individual responses to set questions were reported using the frequency for each response category. Free text responses were reviewed but proved not to be very helpful with no additional information taken from these.

Table 1: Country and job category of respondents.

	Number of respondents $n = 37$
Country	
UK	11
Germany	16
Switzerland	8
France	2
Job Category[*]	
Healthcare organisation, general management	3
Healthcare organisation, research management	5
Healthcare organisation, information governance officer	3
Senior clinical researcher/CTU director	7
Senior informatics staff	4
Healthcare service provider	10
National policy makers	3
National opinion leaders	4
Patient association lead	3
Ethics committee representative	3

[*] Participants may be in more than one category.

8. Results

There were a total of 37 structured interviews conducted by the leads at 7 different pilot sites for EHR4CR in Germany, the UK, Switzerland, and France with the breakdown of personnel type interviewed and their location shown in Table 1. The leads at the centres reported conducting a mix of telephone and face-to-face interviews with each lasting between 60 to 90 minutes, although data on format and timing were not collected.

8.1. Trial Feasibility. Interviewees were unanimous that an EHR4CR platform approach to assessing feasibility would enhance the conduct of clinical trials and a clear majority of responders indicated that they anticipated that this approach would reduce workloads in the assessment of clinical trial feasibility for clinical and research staff at the participating centres (24% Strongly Agree and 47% Agree).

The majority of respondents reported that prior informed consent would not be required (81%), their institution would approve data transfer (81%), and there would be no ethics/information governance concerns (74%) for the return of a single aggregated number of eligible patients as outlined in Scenario A (see Table 2). Scenario B, which suggested returning aggregated numbers for each criterion, had slightly lower levels of support: prior informed consent not needed (70%), institution approved (70%), and no ethics/information governance concerns (65%).

The scenarios suggesting the return of anonymous data to a third party (Scenario C) or the research sponsor (Scenario D) had markedly different results. The respondents reported

Table 2: Use of the EHR4CR platform for trial feasibility.

	Scenario	A	B	C	D
Do you think that data transfer would require previous informed consent by patients for the use of their data in this manner?	Yes	7 (19)	10 (27)	25 (68)	29 (78)
	No	30 (81)	26 (70)	8 (22)	5 (14)
	Do not know	0	1 (3)	3 (8)	3 (8)
Do you think that data transfer would be approved by your institution (or an institution in your country if you are not based in a healthcare institution)/by an ethics committee in your country?	Yes	30 (81)	26 (70)	16 (43)	12 (32)
	No	3 (8)	5 (14)	9 (24)	15 (41)
	DK	1 (3)	2 (5)	8 (22)	6 (16)
Do you think that the transfer of these data would create ethical/information governance concerns at your institution (or an institution in your country if you are not based in a healthcare institution)?	Yes	7 (21)	7 (21)	22 (65)	29 (85)
	No	25 (74)	22 (65)	7 (21)	2 (6)
	DK	1 (3)	4 (12)	4 (12)	2 (6)
	Strongly Agree	Agree	Neither	Disagree	Strongly Disagree
Indicate your agreement/disagreement with the statement that "this approach to facilitating feasibility assessment would enhance the conduct of clinical trials."	0	3 (100)	0	0	0
Indicate your agreement/disagreement with the statement that "providing data to an organisation conducting clinical research or trusted third party in such an automated manner would reduce workloads and save time of healthcare institution employees."	8 (24)	16 (47)	6 (18)	4 (12)	0

Scenario A: total number of patients meeting all criteria only returned to sponsor.
Scenario B: number of patients meeting each criterion returned to sponsor.
Scenario C: number of patients meeting each criterion returned to 3rd party.
Scenario D: deidentified patient records meeting criteria returned to sponsor.

that prior informed consent would be needed (68%), less than half felt their institution would approve data transfer (43%), and there would be ethics/information governance concerns (65%) using a third party to host data. Returning data to the research sponsor would need prior informed consent (78%), less than half felt their institution would approve data transfer (41%), and the vast majority suggested there would be ethics/information governance concerns (85%).

8.2. Trial Recruitment. The majority of respondents (70%) thought that using EHR4CR for recruitment to trials would be approved by healthcare organisations in their country and that these approaches would also enhance the conduct of trials (67%) (see Table 3). However, approximately 50% of responders thought that using EHR4CR for recruitment would create either ethics or information governance concerns in their country and would require prior informed consent (51%) and prior regulatory approval (57%).

8.3. Facilitating Trial Execution. The respondents reported that using EHR4CR to extract data from the patient's electronic records to the trial dataset would be approved by healthcare organisations in their country (70%) and would not raise ethics/information governance concerns (71%) (see Table 4). There was less support for the transfer of trial data back to the patient's record: only 49% thought it would be approved by their institution, whilst 47% thought it would raise ethics/information governance concerns. Respondents suggested the transfer of trial specific data into electronic health records could lead to some concerns for treating physicians (65%) but this could be reduced by holding this data separately (59%).

8.4. Adverse Event Reporting. Using EHR4CR to facilitate adverse event reporting was widely accepted as enhancing trials (see Table 5). Although only 50% were confident that this would receive ethical approval for return of all data to the research sponsor (Scenario H), this increased if data were dealt with by a local clinician (Scenario I, 70%) or to the regulatory authority (Scenario J, 59%). Half (50%) of respondents thought returning adverse event reporting data to the research sponsor would raise ethics/information governance concerns, but this reduced to a quarter (24%) if returned to a local clinician (24%) or a third (32%) if returned to the regulatory authority (32%).

9. Motivations and Threats

The strongest motivating factors for future participation in an EHR4CR platform (see Table 6) were income generation from industry trials (Strongly Agree 16% and Agree 54%), providing patients with faster access to novel medicines (Strongly Agree 27% and Agree 46%), stimulus for the development of local health information systems (Strongly Agree 22% and Agree 51%), improved quality of healthcare data (Strongly Agree 38% and Agree 41%), potential to use the platform for academic studies (Strongly Agree 35% and Agree 49%), improvement in the quality (Strongly Agree 32% and Agree 46%), and efficiency (Strongly Agree 30% and Agree 54%) of trials. The biggest threats raised to the success of EHR4CR were considered to be the inadequacy

Table 3: Use of the EHR4CR platform for trial recruitment (Scenario E).

	Yes		No		DK
Indicate whether you think that this scenario would require previous informed consent by patients for the use of their data by the investigator/by the healthcare team.	19 (51)		16 (41)		1 (3)
Indicate whether you think that this scenario would require previous authorisation from data protection authority or another external regulatory body.	21 (57)		11 (30)		4 (11)
Do you think that this scenario would be accepted by your institution (or an institution in your country if you are not based in a healthcare institution)/do you think, in your opinion, that this scenario would be approved by an ethics committee in your country?	26 (70)		6 (16)		5 (14)
Indicate your agreement/disagreement with the statement that "this approach to facilitating patient recruitment would enhance the conduct of clinical trials."	Strongly Agree 0	Agree 2 (67)	Neither 1 (33)	Disagree 0	Strongly Disagree 0
Do you think that this scenario would create ethical/information governance concerns at your institution (or an institution in your country if you are not based in a health care institution)?	Yes 17 (50)		No 16 (47)		DK 1 (3)
Indicate your agreement/disagreement with the statement that "this approach to facilitating patient recruitment would reduce workloads and save time of healthcare institution employees."	Strongly Agree 11 (32)	Agree 18 (53)	Neither 4 (12)	Disagree 0	Strongly Disagree 0

of local health information systems (Strongly Agree 16% and Agree 43%); missing key data items (Strongly Agree 16% and Agree 46%); the cost of upgrading local system environments (Strongly Agree 32% and Agree 27%), and ethical (Strongly Agree 8% and Agree 49%), data protection (Strongly Agree 11% and Agree 46%), and information governance (Strongly Agree 14% and Agree 51%) concerns.

10. Discussion

The overwhelming message from stakeholder engagement was the positive support for the proposed EHR4CR platform to enhance the conduct of feasibility assessments and the recruitment of study subjects and thereby to improve the conduct of clinical trials. However respondents highlighted that the platform may raise ethical and governance concerns in all areas and failing to meet these requirements would constitute major threats to the project. The requirement for regulatory and institutional support within the proposed feasibility scenarios suggested strongly that patient data should not be transferred outside the host institution and also that patients should be given an opportunity to opt out of use of their EHR.

Stakeholder support for the project was shown through agreement that it would improve the local quality of care offered to patients, could improve local health systems, and would help patients get access to new medications faster. Increased participation for local centres in trials and additional financial benefits associated with this were also highlighted, although few stakeholders suggested these as reasons to participate.

The EHR4CR stakeholder engagement raised many important issues about governance, privacy, and data management and data standards. The development of the EHR4CR project and how it addressed these barriers and challenges will provide information to influence future developments in big healthcare databases. With the ultimate goal of improving clinical trials in the European Union, the project provides a unique opportunity to coordinate important stakeholders' efforts to create new clinical trials environments.

11. Strengths and Limitations of the Work

Although this survey was targeted at informing the design and governance of the EHR4CR platform, the scenarios and the interview questions were posed in a generic form which relates to the use of hospitals electronic health record system to support the design, recruitment, and conduct of clinical trials. Interviewees therefore did not need to have a detailed understanding of the project or its particular technical implementation in order to respond to the survey.

The seniority of the individuals invited for interview and the length of the interview (often between 60 and 70 minutes) will have placed practical limits on the number of participants per country, and the number of countries which could be included in this survey. The interviews were arranged and conducted by senior academics who were aware of the potential risk of bias and each deliberately sought to invite interview senior individuals who were not otherwise connected with the project or with the partner organisations in the consortium but would be important decision makers or decision influences in the wider acceptability of the proposed

Table 4: Use of the EHR4CR platform for trial execution.

	Scenario	F	G
Do you think that this scenario would be accepted by your institution (or an institution in your country if you are not based in a healthcare institution)/do you think that this scenario would be approved by an ethics committee in your country?	Yes No DK	26 (70) 4 (11) 5 (14)	18 (49) 10 (27) 5 (14)
Indicate your agreement/disagreement with the statement that "this approach to facilitating trial conduct would enhance the quality of clinical trials."	Strongly Agree Agree Neither Disagree Strongly Disagree	0 1 (33) 2 (67) 0 0	1 (33) 0 0 2 (67) 0
Do you think that this scenario would create ethical/information governance concerns at your institution (or an institution in your country if you are not based in a healthcare institution)?	Yes No DK	8 (24) 24 (71) 1 (3)	16 (47) 14 (41) 2 (6)

Indicate how much you would support the statement that "extraction of data automatically from the electronic patient record into a trial database would reduce workloads and save time of healthcare institution employees."	Strongly Agree 19 (56)	Agree 8 (24)	Neither 3 (9)	Disagree 2 (6)	Strongly Disagree 0

	Yes	No	DK
Do you think that this scenario could create concerns that the additional information might be misunderstood by other physicians treating the patient due to unfamiliar measurements or measurements obtained by unfamiliar methods?	24 (65)	9 (24)	1 (3)
Do you think that this scenario would create fewer concerns if the additional information was separated from the usual patient record?	22 (59)	8 (22)	4 (11)

Scenario F: extraction of data from the patient record.
Scenario G: transfer of trial specific data to the patient's electronic record.

Table 5: Use of the EHR4CR platform for adverse event reporting.

	Scenario	H	I	J
Do you think that this scenario would be accepted by your institution (or an institution in your country if you are not based in a healthcare institution)?/do you think that this scenario would be approved by an ethics committee in your country?	Yes No DK	19 (51) 9 (24) 7 (19)	26 (70) 4 (11) 5 (14)	22 (59) 4 (11) 7 (19)
Do you think that this scenario would create ethical/information governance concerns at your institution (or an institution in your country if you are not based in a health care institution)?	Yes No DK	17 (50) 16 (47) 0	8 (24) 22 (65) 3 (9)	12 (32) 21 (57) 2 (5)
Indicate your agreement/disagreement with the statement that "accumulating adverse event reports in this manner will significantly improve the reporting of adverse drug reactions during clinical trials"/indicate your agreement/disagreement with the statement that "this approach to facilitating adverse event reporting would enhance the evaluation of the safety of medicines."	Strongly Agree Agree Neither Disagree Strongly Disagree	7 (19) 18 (49) 10 (27) 1 (3) 1 (3)	15 (41) 16 (43) 4 (11) 0 1 (3)	8 (22) 17 (46) 7 (19) 4 (11) 0
Indicate whether you think that this scenario would require previous informed consent by patients for the use of their data.	Yes No DK		17 (46) 15 (41) 3 (8)	12 (32) 21 (57) 2 (5)

Scenario H: individual patient level data on adverse events returned to organisation conducting research.
Scenario I: individual patient level data on adverse events returned to local clinician to prepare report for regulatory authorities.
Scenario J: periodic aggregated data on adverse events reported turned to regulatory authorities.

Table 6: Motivators and threats for participation in EHR4CR.

Use of existing national datasets of deidentified data					
Do you think that out-licensing from your institution (or from an institution in your country if you are not based in a healthcare institution) of a large body of detailed pseudoanonymised longitudinal secondary care (hospital) data to an organisation conducting research into postmarketing drug safety would:	Yes	No	Do not know		
(a) Require prior patient level consent?	22 (59)	14 (38)	0		
(b) Be likely to receive institutional approval?	22 (59)	6 (16)	8 (22)		
(c) Raise significant ethical/information security concerns?	21 (57)	14 (38)	1 (3)		
(d) Require data protection authority or another regulatory external body approval?	26 (70)	5 (14)	4 (11)		
Other aspects					
Indicate your agreement/disagreement with the following as strong motivating factors for your institution's participation in the EHR4CR platform (now or in the future). If you are not based in a healthcare institution, consider these factors for an institution in your country.	Strongly Agree	Agree	Neither	Disagree	Strongly Disagree
Increased income generation from participation in more industry trials	6 (16)	20 (54)	1 (3)	5 (14)	4 (11)
Pressure from government or institution to participate in more pharma industry studies	6 (16)	8 (22)	8 (22)	11 (30)	3 (8)
Providing patients with faster access to new generation medicines	10 (27)	17 (46)	4 (11)	3 (8)	2 (5)
Development of local health information systems	8 (22)	19 (51)	6 (16)	1 (3)	2 (5)
Improvement of local data quality and healthcare	14 (38)	15 (41)	3 (8)	3 (8)	1 (3)
The potential to use EHR4CR platform to conduct academic studies	13 (35)	18 (49)	3 (8)	1 (3)	0
Opportunity to improve the quality of data in clinical trials	12 (32)	17 (46)	3 (8)	3 (8)	1 (3)
Opportunity to improve the efficiency of clinical trials	11 (30)	20 (54)	5 (14)	0	0
Indicate your agreement/disagreement with the following as significant threats in your institution or country to the success of EHR4CR.					
Inadequate availability of key data fields in the patient record	6 (16)	16 (43)	6 (16)	6 (16)	3 (8)
Missing data in the patient record	6 (16)	17 (46)	7 (19)	7 (19)	0
Inadequacy of local health information systems	6 (16)	16 (43)	2 (5)	10 (27)	2 (5)
Cost of upgrading local systems to be compatible with EHR4CR	12 (32)	10 (27)	9 (24)	6 (16)	0
Ethical committee concerns	3 (8)	18 (49)	4 (11)	11 (30)	1 (3)
Local information governance concerns	5 (14)	19 (51)	4 (11)	9 (24)	0
Data protection authorities	4 (11)	17 (46)	5 (14)	7 (19)	2 (5)
Concerns of hospital management	2 (5)	13 (35)	8 (22)	13 (35)	1 (3)
Concerns of patients	3 (8)	11 (30)	5 (14)	16 (43)	2 (5)
Concerns of clinicians	0	13 (35)	5 (14)	16 (43)	3 (8)

approach. Nevertheless it is recognised that this survey was by invitation and that this sample cannot be claimed to be fully representative of the stakeholder groups included.

12. Comparison to the Literature

There are a number of other initiatives looking to improve clinical research through innovative uses of routine data. The Sentinel Initiative was launched by the FDA in 2008, to develop and implement a proactive system to track the safety of drugs, biologics, and medical devices once they reach the market. It uses preexisting electronic healthcare data at collaborating institutions by running a centrally developed computer program at each site which returns summary results to the organising centre [12]. The system has been used effectively in a number of recent drug safety studies [13–15].

Other initiatives include the Observational Medical Outcomes Partnership (OMOP) [16] and SHRINE [17], which are public-private partnerships built upon the use and sharing of information from existing observational databases. The development of initiatives such as these would suggest that the question is no longer whether but rather how clinical data should be shared to foster innovation and support clinical research [18].

However, it is still unknown how the process of data sharing can become routine, how to define responsible data sharing, which principles to establish, and how to set policies across different countries where interpretations of clinical and information governance may vary and where attitudes

towards reuse of routinely collected clinical data may differ. The EHR4CR project may be one of the milestones on the road ahead.

13. Conclusions

There was clear support for the overall objectives of EHR4CR and a belief that a well-developed EHR4CR platform would reduce workloads and improve the conduct and quality of trials. However, the interviewees did raise some ethical and information governance concerns and threats to the potential success of an EHR4CR platform including that only aggregated data should be reported for trial feasibility, that prior ethics approval may be required for use of patient's EHR for recruitment, and that the combination of trial data with patient EHR could generate new issues and concerns. This study has helped guide the development of the EHR4CR informatics platform and highlight areas where there is a need to clarify and emphasise data security, privacy, and information governance issues in the roll-out of the platform.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

Translational Medicine and Patient Safety in Europe: TRANSFoRm—Architecture for the Learning Health System in Europe

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The Learning Health System (LHS) describes linking routine healthcare systems directly with both research translation and knowledge translation as an extension of the evidence-based medicine paradigm, taking advantage of the ubiquitous use of electronic health record (EHR) systems. TRANSFoRm is an EU FP7 project that seeks to develop an infrastructure for the LHS in European primary care. *Methods*. The project is based on three clinical use cases, a genotype-phenotype study in diabetes, a randomised controlled trial with gastroesophageal reflux disease, and a diagnostic decision support system for chest pain, abdominal pain, and shortness of breath. *Results*. Four models were developed (clinical research, clinical data, provenance, and diagnosis) that form the basis of the projects approach to interoperability. These models are maintained as ontologies with binding of terms to define precise data elements. CDISC ODM and SDM standards are extended using an archetype approach to enable a two-level model of individual data elements, representing both research content and clinical content. Separate configurations of the TRANSFoRm tools serve each use case. *Conclusions*. The project has been successful in using ontologies and archetypes to develop a highly flexible solution to the problem of heterogeneity of data sources presented by the LHS.

1. Introduction

The Learning Health System (LHS) describes an approach to improve healthcare that is solidly founded on the creation and use of knowledge; "health" as opposed to "healthcare" is sometimes used to emphasise the role of consumers as cocreators and users of health knowledge [1]. The development of the LHS is a natural outcome of the evolution of evidence-based medicine (EBM). Based on the greater utilisation of electronic health records (EHRs) and on novel computing paradigms for data analysis, the LHS provides potential solutions for the glacial slowness of both the traditional research process and the research translation into improved care [2].

EBM is focused on generating medical evidence and using it to make clinical decisions. The highest level of

evidence, level 1 evidence of the effectiveness of a healthcare intervention in EBM, consists of a meta-analysis of randomised controlled trials (RCTs) [3]. However, RCTs are complex and extremely expensive, the result being that much of healthcare remains unsupported by high quality evidence. Furthermore, RCTs themselves are prone to bias and manipulation in the choice of eligible subjects, comparators, and outcome measures [4]. One solution has been to carry out light touch and simple, termed "pragmatic" RCTs with very inclusive eligibility criteria and followup via routine data collection. It is those kinds of RCTs that lend themselves most to incorporation into a LHS.

There is also potential to replace RCTs with analysis of routine data, using techniques such as instrumental variables and propensity scores to control for bias [5]. Much future research is needed to define when routine data could be a sufficient answer to a problem and when an RCT is required. Furthermore, healthcare practice is not solely limited to interventions, but diagnosis and prognostication play essential parts and are underpinned by prospective cohort evidence. Again, routine data could play a significant role in replacing time-consuming and costly cohort designs.

Primary healthcare is the first point of contact with health services of patients with undifferentiated problems and also provides continuing care for patients with chronic diseases and follows families from "cradle to grave." These functions present a particular problem for EBM. The vast majority of research, be it diagnostic or intervention based, takes place in specialist centres and in highly selected populations [6]. Diagnostic features are not portable across populations with different prevalence and spectrum of disease. Likewise, patients in RCTs are younger and fitter, take fewer drugs concurrently, and have less comorbidity than typical primary care populations. Therefore, many RCTs suffer from limited external validity [7].

Even if appropriate research evidence exists, it is unlikely to be available at the point of care. Early formulations of EBM typically applied to the highly motivated clinician who formulates questions during clinical practice and searches for evidence. Indeed, Professor Sackett's team at Oxford developed an "evidence cart" for ward rounds, with a copy for MEDLINE and a projector to assist in this process in real time [8]. Over the subsequent years, the process of knowledge translation has become formalised: guidelines are explicitly built on systematic reviews of the best available evidence and are refined down to a series of statements to support clinical care, with an associated level of supporting evidence and strength of recommendation [9]. However, even in countries like the UK, where a national agency (National Institute for Health and Care Excellence) is funded to carry out this process, guidelines may only be updated once in a decade. Increasingly, the number of potential guidelines applicable to a given patient at a given point on the care pathway becomes a problem of memory and prioritisation for the clinician, let alone the patient. The LHS offers a potential means of using highly advanced electronic triggers to help with advising when one treatment or diagnosis is favoured. It should also be possible to reintroduce patient choice by explicit weighting of options using patient-derived outcome data.

The LHS concept is still in its infancy, and much needs to be done to explore and demonstrate the potential for using an advanced digital infrastructure to support the LHS. The FP7 TRANSFoRm project (http://www.transformproject.eu/) was funded via the Patient Safety Stream of ICT for Health. Efficient research design and knowledge translation are a core underpinning of safe clinical practice. It is not good enough to simply avoid error, defined as care that falls well below the average standard, but clinicians should be seeking optimal care for their patients. The LHS, at its barest essential, is all about promoting optimal care. The TRANSFoRm project aimed to develop and demonstrate methods, models, standards, and a digital infrastructure for three specific components of the LHS:

(1) genotype-phenotype epidemiological studies using multiple existing primary care and "biobank" genomic datasets;

(2) RCTs with both data and trial processes embedded within the functionality of EHRs and the ability to collect Patient Reported Outcome Measures (PROMs) on demand;

(3) decision support for diagnosis, based on clinical prediction rules (best diagnostic evidence) and fully integrated with a demonstrator EHR system.

2. Methods

Each specific clinical "use case" (shown below) served four purposes: initial requirements elicitation; detailed modelling of infrastructure and required data elements; design of concurrent validation and evaluation studies; and final clinical demonstrations. 21 partner organisations in ten EU member states took part in the project, over five years. At the time of writing, the project has 11 months to run and the final evaluation and clinical studies are about to commence.

TRANSFoRm Use Cases

Diabetes Use Case. The aim of the Diabetes use case is to enable a distributed query to look for eligible patients and extract data from multiple federated databases. In the pilot study, the query will define patients and data to support analysis of the relationship between well-selected single nucleotide polymorphisms (SNPs) in type 2 diabetic patients and the response to sulfonylurea.

GORD Use Case. The aim of the GORD use case is to investigate the effectiveness of on demand versus continuous use of proton pump inhibitors on reflux symptoms, quality of life, and self-rated health in patients with gastrooesophageal reflux disease in primary care. The study will be conducted in five localities (UK: two vendors, Poland, Netherlands, and Crete) and it will aim to recruit, randomise, and follow 700 patients at 40 primary care centres using the clinical trial application.

Diagnosis Use Case. The aim of the diagnosis use case is to provide integrated point-of-care decision support for patients

presenting with chest pain, abdominal pain, and shortness of breath.

TRANSFoRm aims to produce a highly flexible infrastructure that presents the lowest possible barriers to entry for EHR systems and datasets, but at the same time it makes the maximum use of the existing data standards and methods for managing heterogeneity, both structural and terminological, between data sources. A basic principle of the TRANSFoRm project was to use available standards and models as much as possible and integrate them into the TRANSFoRm infrastructure. It was decided early on in the project that TRANSFoRm would take a model-based approach, using 4 models to capture (1) clinical meaning, (2) research meaning, (3) provenance, and (4) diagnostic meaning. The latter is essentially a subset of the clinical model, but it was modelled separately for efficiency. The archetype approach of constraining one model against the other, in a two-level design (clinical and research), was used to describe data elements [10]. Where available, existing tools for building and maintaining models as an ontology were used, although we presented a novel use of LexEVS, which we employed to support both structural and semantic models [11].

Clinical concepts were modelled using an ontology (termed the Clinical Data Information Model, CDIM) [12]. Additional semantic detail for data elements was expressed by using LexEVS to support binding of terminology terms to CDIM expressions. For representation of research processes, we extended an existing domain model, the Primary Care Research Object Model, adding objects primarily in the clinical area [13]. The resulting Clinical Research Information Model (CRIM), in conjunction with CDIM, enabled a two-level archetype to be defined for each required data element in the use cases. In order to define case report forms and study designs for the RCT, we used the CDISC ODM and SDM standards, but adding an archetype approach for the description of the data element "payload" [14].

The intention from the outset with TRANSFoRm was that all models would be published, standards would be reused and adapted as required, the software would reuse the existing open source components, if available, and all TRANSFoRm software components would be made available as open source tools under an "Apache" license. We believe that the value lies in the data and the knowledge generated from it and that amortizing the infrastructure can only act as a potential barrier for realising the value of the data/knowledge.

Evaluation of TRANSFoRm will consist of a technical validation of the TRANSFoRm tools and three clinical and sociotechnical evaluation studies. For the DSS, an evaluation of the system, integrated with the In Practice Systems Vision 3 EHR system, is underway. General practitioners are conducting a simulated clinical session with actors simulating patients presenting with carefully prepared test problems. This is a within-subjects design, with the cases solved first without and then with the DSS and the primary outcome being accuracy. We also measure usability and amount of information coded into the EHR. The Diabetes use case is being evaluated on the basis of performance, as judged by users, of the system in selecting and extracting data from five databases. Accuracy of selecting eligible patients by users employing the TRANSFoRm Query Workbench will be measured. The GORD (gastrooesophageal reflux disease, a disorder caused by the retrograde flow of gastric contents from the stomach into the oesophagus, causing symptoms and/or mucosal damage) study is being conducted as a full clinical RCT (individual subjects randomised) with a nested evaluation study. Principal outcomes of the clinical study are symptom profiles and quality of life measured by PROMs (Patient Reported Outcome Measures) collected on smartphones via a dedicated TRANSFoRm mobile data collection app. The sociotechnical evaluation is a nested cluster trial and will compare recruitment rates, completeness of data, and costs of the TRANSFoRm system compared to usual practice, in this case, a simple web form for the clinical measures and paper questionnaires for the PROMs. The results of the three TRANSFoRm evaluation studies will be available in late 2015.

3. Results

The TRANSFoRm software ecosystem is comprised of a set of generic middleware components that provide essential shared functions for the LHS applications built in TRANSFoRm, namely, secure data transport, authentication, semantic mediation, and data provenance (with respect to processing of data within TRANSFoRm). As LHS is characterized by routine production, transformation, and dissemination of data and knowledge, secure channels and reliable authentication are necessary to ensure confidence and buy-in by the data owners. The data itself resides in a vast array of distributed repositories that vary both in structure and in terminology, making data interoperability a key requirement that TRANSFoRm delivers using a semantic mediation approach combined with the standard data connectivity module (data node connector: DNC). The DNC implements data interoperability, as well as managing workflow processes and data extraction for participating EHRs and data sources, as discussed in the next section. Different flavours of DNC operate in epidemiology and RCT use cases, as the RCT DNC has to support additional requirements of the RCT workflow. Data provenance capture in TRANSFoRm implements traceability, which is necessary both to support trust and transparency and to enable learning and improvement in LHS processes.

On top of these shared components, three application specific tools were built to support the use cases: epidemiological study query workbench, clinical trial monitoring tool, and a diagnostic support plugin for EHR systems.

The high-level overview of the software components is shown in Figure 1.

4. Epidemiological Study Application

The epidemiological study TRANSFoRm software configuration (Figure 2) is used in the genotypic-phenotypic T2D study use case and consists of tools for secure, provenance-enabled design and execution of eligibility queries and data extractions from heterogeneous data sources. Eligibility queries are

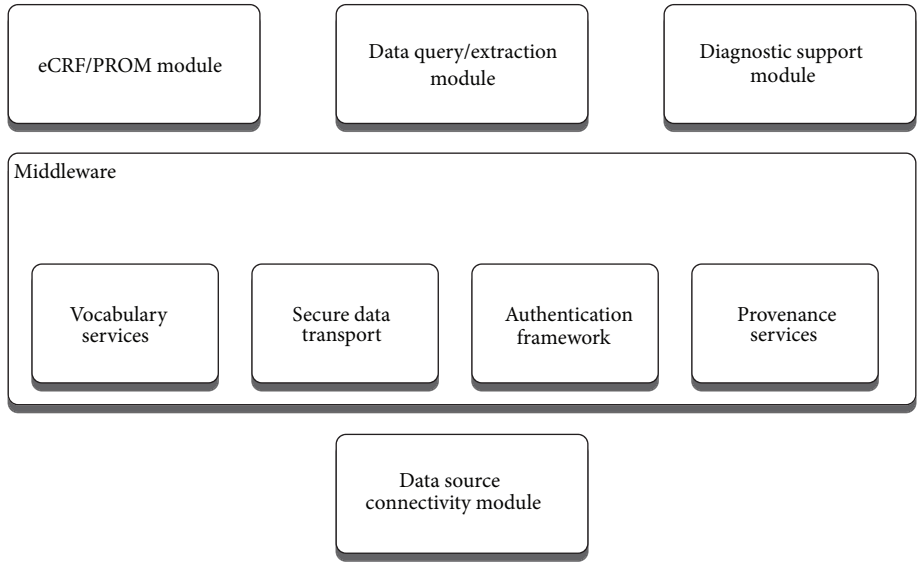

Figure 1: High-level software components.

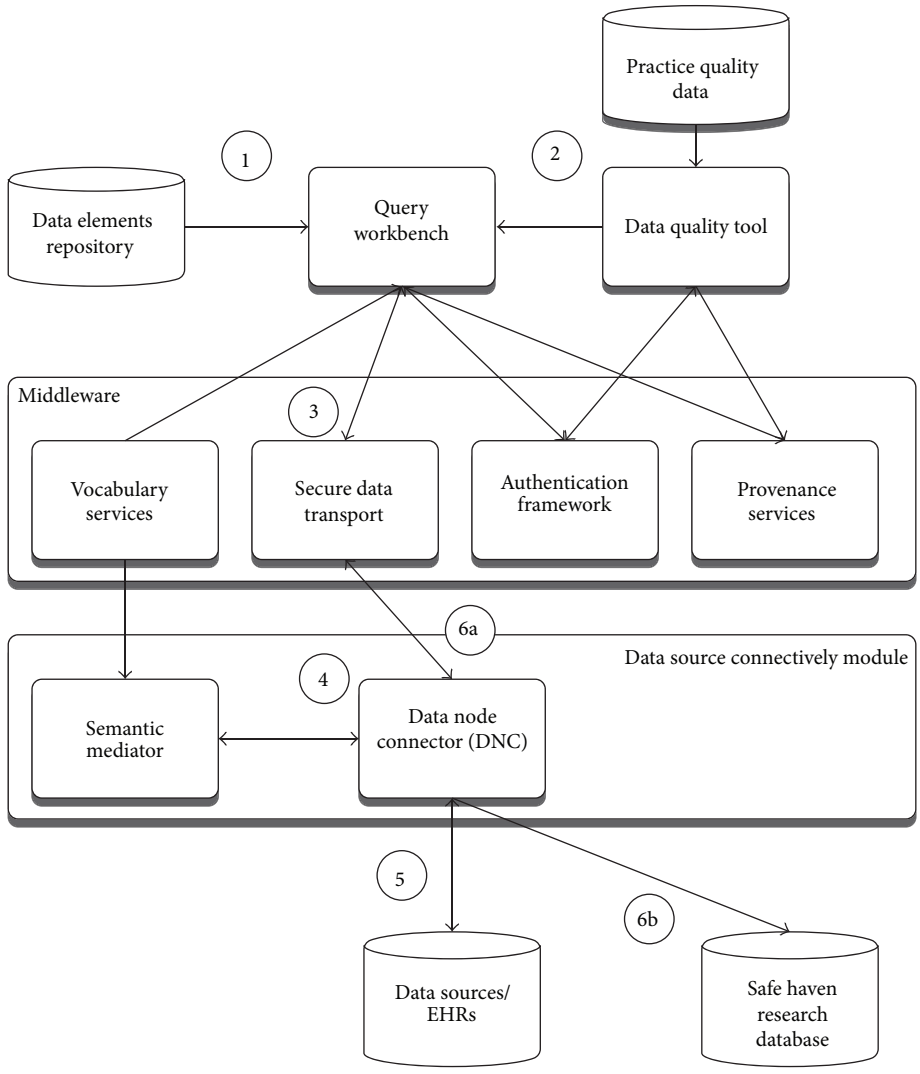

Figure 2: Epidemiological study configuration annotated with steps in the query process.

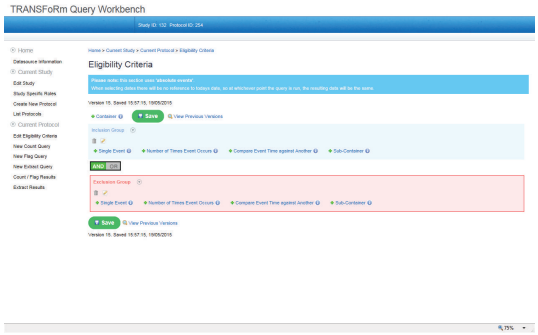

Figure 3: TRANSFoRm Query Workbench.

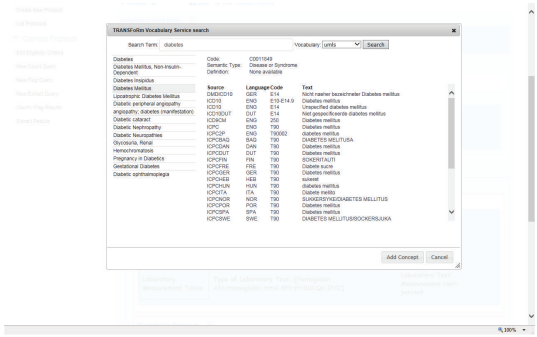

Figure 4: Concept search in TRANSFoRm Query Workbench.

formulated by the researcher in the query workbench (QWB) web tool (Figure 3) using model-based constructs (Figure 2, step 1). QWB users enter clinical terms into the system which then presents the user with a list of corresponding concepts from standard terminologies and classifications (Figure 4). The researchers are able to use a data quality tool, storing metadata about available practices and data that reside in them, to restrict the search to practices with a high registration percentage of the variables targeted in the study (step 2). The queries are dispatched to the data sources via the middleware (step 3) to the local data node connector. This is a TRANSFoRm component that sits at the data source and translates the generic CDIM-based query into a local representation using the semantic mediator component (step 4) and subsequently presents that locally interpretable query either to the data source directly or to a human agent for final approval (step 5), before returning the result. Three types of queries are supported: patient counts, flagging patients, and data extraction. Results of count and flag queries are sent back to the query workbench via the middleware (step 6a) and can be viewed by the researcher in the QWB web tool. The patient data extraction result is passed to a safe haven (step 6b), accessible only to the authorised researcher, using the appropriate secure data transport mechanism.

5. Clinical Trial Application

The clinical trial software configuration (Figure 5) is used in the GORD use case and consists of components needed for design, deployment, and collection of trial data, backed by provenance and secure authentication framework for researchers. The trial data collection is supported using electronic Case Report Forms (eCRFs) and Patient Reported Outcome Measures (PROMs). The former are filled in via a web browser by the clinician, while the latter are completed by the patients using either web or mobile devices. Also supported is the orchestration of data collection across multiple clinical sites where the trials are taking place.

The TRANSFoRm architecture delivers important components of clinical trials: patient eligibility checks and enrolment, prepopulation of eCRF data from EHRs, PROM data collection from patients, and storing of a copy of study data in the EHR. The key component of the architecture is the TRANSFoRm Study System (TSS) that coordinates study events and data collections, using HTML form templates with bound queries for preloading data from the EHR. The studies, represented using a custom extension of CDISC SDM/ODM standard, are loaded into the TRANSFoRm Study System (step 1). Whenever an interaction is required between the Study System and EHR, for example, eligibility checks or partial filling of eCRF forms form EHR data, a query is fired off to the EHR via the data node connector (step 2). As in the epidemiological study configuration, the DNC acts as a single point of contact of TRANSFoRm components and the local EHR. In addition to translating and sending queries to the EHR (step 3), the DNC acts as a web server that displays eCRF forms for the clinician to fill with study-required information not present in the EHR. Once completed, the form is submitted to both the study database and the EHR for storage considering requirements for eSource data use in clinical trials (step 4). The message protocol for this interaction is currently undergoing comparison evaluation with the IHE standards [17]. The PROM data is collected directly from the patients using web or mobile devices (step 5). The software configuration for the GORD study undergoes a formal Computer System Validation (CSV) process including qualifications for installation, operation, and performance to ensure that study system and study process have been Good Clinical Practice- (GCP-) validated prior to being employed in the GORD clinical trial use case. Because of the narrow connection between EHR and study system, part of GCP-validation is the assurance of data privacy and confidentiality of the personal patient data.

6. Diagnostic Support Application

Diagnostic support software configuration (Figure 6: diagnostic support configuration) consists of tools for mining new rules from health data sources and managing their deployment into the knowledge base, upon which an evidence service is operating to drive a diagnostic support tool embedded into a local EHR system.

The primary function of the tool is to suggest to clinicians diagnoses to consider at the start of the clinical encounter based only on the existing information in the patient record and the current reason for encounter [18]. It also allows bottom-up input of observed patient cues (symptoms and signs), independent of associated diagnosis, or top-down

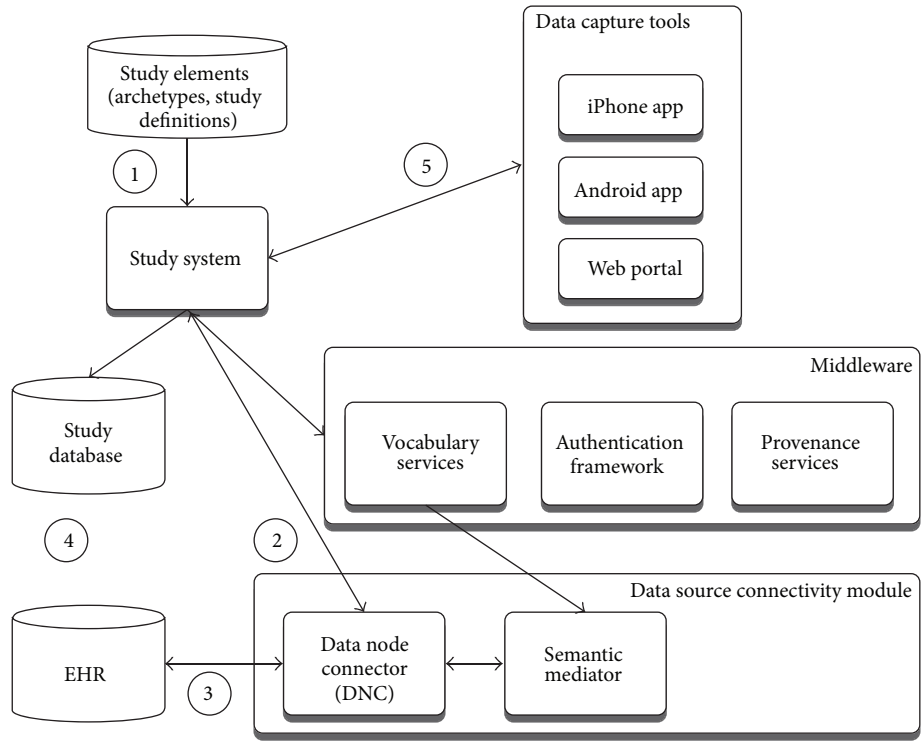

Figure 5: TRANSFoRm clinical trial configuration.

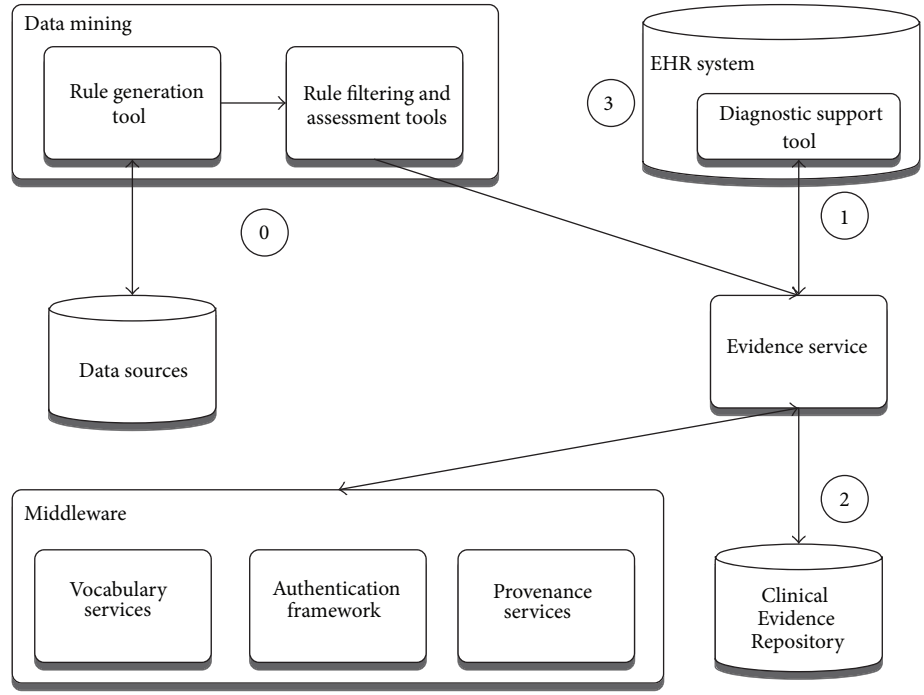

Figure 6: Diagnostic support configuration.

drilling into and selection of cues supporting specific diagnoses.

The rules used in the diagnostic process are generated by data mining tasks (step 0), which get manually curated and fed through the evidence service into the Clinical Evidence Repository. When the patient presents, the cues entered or selected are then used to dynamically rank the potential differential diagnoses (Figure 7). This is done by the DSS plugin embedded into the EHR, sending data to the evidence service (step 1), which queries the rules stored in

Table 1: A table of outputs and exploitation plans.

TRANSFoRm output	Exploitation plan
(1) Privacy model: a "zone" model with an explicit method of graphically depicting the zones and operation of filters between zones	Published method [15]
(2) Provenance infrastructure: based on the Open Provenance Model [REF], each infrastructure component captures a provenance trace that enables reconstruction of an audit trail for any given data element	Published method [16]
(3) Clinical prediction rule ontology based web service	The diagnostic ontology has been made available as a public download in OWL format on the TRANSFoRm website (http://www.transformproject.eu/). A future project is required to extend the data beyond the three initial reasons for encounter
(4) Research data model	CDIM [12] and CRIM [13] have been published. A full description of the use of CDIM and CRIM in the construction of data node connectors will be published and made available on the TRANSFoRm website
(5) eCRF	Extension of CDISC ODM and SDM by the incorporation of archetypes with references to the CRIM and CDIM models will be published and discussions are ongoing with CDISC regarding future incorporation into the standards. A reference implementation of the clinical trial system will be maintained within the European Institute. At present, individual archetypes have to be written by hand; discussions are in hand for the production of an archetype authoring tool
(6) Data federation	A reference implementation of the genotype-phenotype study system will be maintained within the European Institute. Search authoring tools will be available open source
(7) DSS integration	The DSS is currently integrated with the InPS Vision 3 system. Further work is required to move this to a data node connector/CDIM-based flexible system

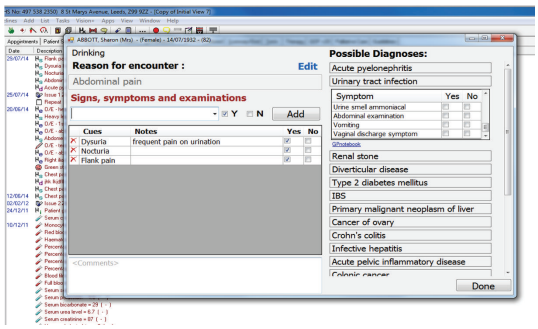

Figure 7: Diagnostic support tool implemented as a plugin to InPS Vision EHR system.

the Clinical Evidence Repository (step 2), before sending the potential diagnoses back, annotated with levels of support and confidence for the presenting case. Upon exiting the tool, the coded evidence cues and current working diagnosis can be saved back to the patient EHR (step 3).

7. Conclusions

TRANSFoRm demonstrated how a Learning Health System can be implemented in European clinical research and practice. The full list of project outputs and the exploitation plan for each are shown in Table 1 and promoted via an open source model. TRANSFoRm will be a full participant in the European Institute for Innovation through Health Data and will make its tools and models available via the institute. In addition, we are internationally active as participants and promoters of the Learning Healthcare System. Via the LHS, we are publishing models, standards, and tools to the world research community. The UK serves as an exemplar of our business model, with multiple EHRs participating in the project as well as the Medicines and Healthcare Products Regulatory Agency, Clinical Practice Research Datalink (CPRD). CPRD currently extracts data from practices to a total population of 8 million and links them to 20 other health datasets. CPRD will be using the TRANSFoRm clinical trial tools, in conjunction with additional reworking by a commercial

software vendor to create a full EHR-embedded clinical trial facility for the UK Clinical Research Network.

Disclaimer

The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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Research Article

User Satisfaction Evaluation of the EHR4CR Query Builder: A Multisite Patient Count Cohort System

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The Electronic Health Records for Clinical Research (EHR4CR) project aims to develop services and technology for the leverage reuse of Electronic Health Records with the purpose of improving the efficiency of clinical research processes. A pilot program was implemented to generate evidence of the value of using the EHR4CR platform. The user acceptance of the platform is a key success factor in driving the adoption of the EHR4CR platform; thus, it was decided to evaluate the user satisfaction. In this paper, we present the results of a user satisfaction evaluation for the EHR4CR multisite patient count cohort system. This study examined the ability of testers ($n = 22$ and $n = 16$ from 5 countries) to perform three main tasks (around 20 minutes per task), after a 30-minute period of self-training. The System Usability Scale score obtained was 55.83 (SD: 15.37), indicating a moderate user satisfaction. The responses to an additional satisfaction questionnaire were positive about the design of the interface and the required procedure to design a query. Nevertheless, the most complex of the three tasks proposed in this test was rated as difficult, indicating a need to improve the system regarding complicated queries.

1. Background

Clinical trials (CTs) are essential to assess the effectiveness and safety of new treatments and procedures. The cost and complexity of CTs have increased in the last decades [1] and initial budgets are often readjusted upwards due to recruitment rates not being met [2] and costly protocol amendments [3].

Optimized protocol designs have proven to be essential in avoiding such issues and ensuring CT success [4]. Study protocol design is the first step in every CT, in which the purpose and detailed methods needed to carry out a certain CT are established. Current protocol design processes include interaction with clinicians located at clinical research institutions, who give their expertise on fundamental matters of protocol design, such as the viability of the trial and the number of possible participants at their site. The responses given by clinicians to these questions are usually obtained through electronic or paper based feasibility assessments, an often slow and cumbersome process, seldom supported by efficient electronic systems. Furthermore, responses from the clinicians are in the majority of the cases based on subjective experience rather than on historical evidence [5].

Some initiatives are trying to improve the design of study protocols through the reuse of Electronic Health Records (EHRs) to automate certain process steps. For example, the Shared Health Research Information Network (SHRINE) provides a query tool for open source Informatics for Integrating Biology and the Bedside (i2b2) clinical data repositories [6]. Other examples of the reuse of clinical data to support clinical research include the feasibility platform for stroke studies (FePASS), an open access online web-system that allows users to obtain eligible patient counts for stroke trials based on user-defined eligibility criteria (EC)

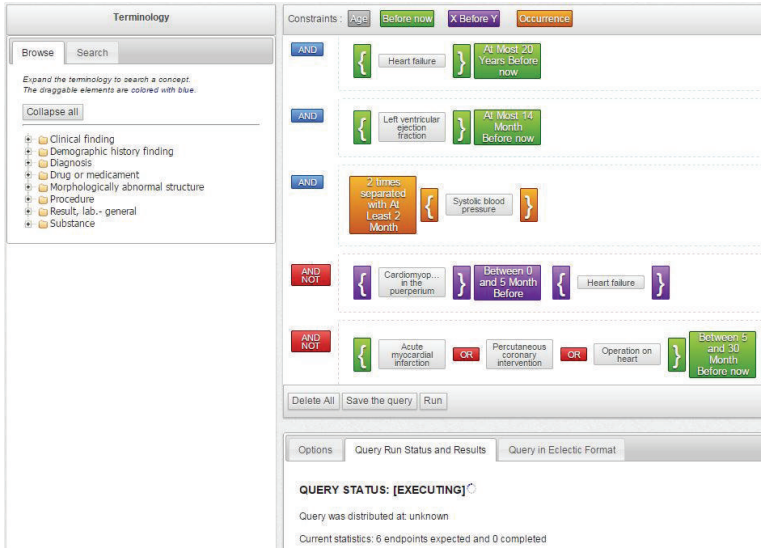

Figure 1: EHR4CR Query Builder. Example of a query built using the EHR4CR QB. The terminology services can be found on the left part of the image and the selected elements and logic on the right part. On the right bottom corner, the user can see the status of the query, the options for each criterion, and the visualisation of the EC in human readable language.

[7] and the Feasibility Assessment and Recruitment System for Improving Trial Efficiency (FARSITE) tool [8]. These systems often have limitations such as reduced number of temporal constraints available or single source compatibility [9]. Several electronic systems provide support for different process steps of CTs, especially for the case report form completion and the serious adverse event reporting, but there is a need for a single platform that covers a broader variety of the CT process steps [10]. Due to these reasons and limitations, the Innovative Medicines Initiative (IMI) started the Electronic Health Records for Clinical Research (EHR4CR) project (http://www.ehr4cr.eu/) in 2010. The EHR4CR project aims to support the CT steps of protocol feasibility (PF), patient identification and recruitment (PIR), clinical trial execution, and serious adverse event reporting. The EHR4CR technological platform currently supports the PF through the EHR4CR Query Builder (QB), a web-based Java platform with a drag and drop graphic interface (see Figure 1) that allows users to design queries based on CT inclusion and exclusion criteria, send these to specific systems at sites from countries initially across Europe, and automatically obtain, within minutes, the objective number of patients per site matching the given criteria. The system preserves the anonymity of patient data through the shift of dates, fuzzing of low counts, and providing only patient counts (PF) or pseudonymised patient names and identifiers (PIR).

The EHR4CR QB contains a central terminology service (see Figure 1) with several hundred elements from the most important medical classifications and terminologies, as well as all the temporal constrains and Boolean logic needed to build feasibility queries [11]. This system is intended to complement contact with clinicians in the protocol design process by providing reliable quantitative data about availability of patient population in dedicated sites [5]. The EHR4CR QB is also being reused in a PIR scenario of the project, in which the EHR4CR QB allows users located at the clinical sites to identify eligible patient candidates for their potential enrolment in a certain CT if confirmed eligible.

In order to support the EHR4CR platform rollout, the reliability, the usability, and the user- friendliness of the system need to be ensured. In this context, usability is understood as "the extent to which a product can be used by specified users to achieve specified goals with effectiveness, efficiency, and satisfaction in a specified context of use" as defined by ISO 9241-11 [12]. For a company interested in becoming users of the system, it is also essential to know what the learning period for the platform is and what the best methods of obtaining user expertise are.

Several tests have demonstrated the reliability of the EHR4CR source code and the algorithm that calculates the patient counts [9]. In a recent evaluation, the effectiveness and the efficacy of the feasibility process using the EHR4CR QB compared with traditional methods were assessed [13]. However, other systems have been proven to be accurate and effective, while the final software was not usable due to its lack of user-friendliness [14]. Thus, there is a need for a user satisfaction evaluation to ensure that the system fits the user needs and an estimation of the training required for the use of the EHR4CR QB in a production environment.

The objectives of this research are therefore to evaluate the user satisfaction of the EHR4CR QB and to assess whether the training material provided is enough to reach an optimal use of the system.

2. Methods

2.1. Study Design. According to Harris et al. [15], the study design of this evaluation is quasi-experimental without control groups, in which the participants first experience the

intervention (here: training of platform), followed by the observation of the outcome (here: suitability of the training based on success of tasks). Since the target population (end users of the EHR4CR QB) did not represent a large number of candidates within the population source, a small sample size was chosen for this evaluation. Thus, a comparison between groups was not considered. To exclude potential bias, an observation-intervention-observation design has been ruled out as well. The study preserved the anonymity of the test persons and it was approved by the Ethics Committee of Münster (Germany).

2.2. Participants. This evaluation was performed in two iterative rounds with professionals familiar with the feasibility domain of clinical research from two different backgrounds: pharmaceutical industry and academia. Representatives of each, involved in the EHR4CR project, were asked to raise awareness among their colleagues. Participants were considered eligible if they (1) had experience in feasibility studies and/or were feasibility managers, (2) did not already know the EHR4CR QB, (3) worked for one of the project partners, and (4) initially agreed on taking the necessary time, answering the usability questionnaire, and recording their computer screen. These potential participants then received a detailed description of the goal, design, overall tasks, tools utilized, data protection, and method of anonymisation of user data via email. They were informed that the participation in this evaluation is completely voluntarily and could be aborted at any time without any consequences.

In the first round, a sample of 22 testers participated, 16 of them belonged to the European Federation of Pharmaceutical Industries and Associations (EFPIA) (http://www.efpia.eu/). The other six participants from academia were a mix of physicians and experts in ergonomics and evaluation of human-machine interfaces and interactions. The pharmaceutical companies represented were Amgen, AstraZeneca, Bayer, GlaxoSmithKline, Lilly, Novartis, and Sanofi. The academic institutions were the Georges-Pompidou European Hospital (HEGP) in Paris and the Evalab from the University Hospitals of Geneva (HUG). All of the institutions (both from academia and from the industry) were members of the EHR4CR consortium. This round was a pretest designed to test the functionality of the system and the study setup and to allow the evaluation team to fix technical issues that users might encounter.

The second round was performed by EFPIA partners (Amgen, Bayer, GlaxoSmithKline, Lilly, and Novartis) only. A sample of 22 completely new testers, familiar with the feasibility domain of clinical research, was recruited, of which 16 participated in this evaluation. For the six other participants, the principal reason for withdrawing was due to scheduling issues. During this round, data for the evaluation was collected.

2.3. Material. A training manual containing 20 pages and an 8-minute-long video produced by the evaluation team were provided to the testers on the day of the evaluation via email. The video was an introduction of the EHR4CR QB demonstrating how to create and execute a query. The training manual produced for the evaluation covered the whole procedure giving step by step details (with illustrating pictures) from connecting to the EHR4CR QB to visualizing the results obtained by the system. The time needed to read it was approximately 20 minutes. Together with the manual, a test instructions document was provided to the participants. These instructions were in the format of a test script that users had to follow to perform the evaluation.

To capture data about the quality of the testing material, the performance of the EHR4CR QB, and the success rate, the testers were asked to take screenshots of their screen after the completion and execution of each query during the testing process. Furthermore, to collect testers' feedback (in terms of interface, ergonomics, and usability of the system) and to assess their satisfaction, a self-hosted installation of the web-based open source survey tool LimeSurvey [16] was utilized to conduct a usability survey by means of a questionnaire. Thus, during the testing, participants were asked to complete the questionnaire after finishing (or cancelling) each task to assess each respective part of the test. They were also asked to rate the training provided prior to testing. This method was meant to collect their immediate impression on the EHR4CR QB and allowed the evaluation team to assess whether the training was sufficient or not.

The questionnaire was based on the System Usability Scale (SUS) [17]. Since the SUS did not cover all objectives of this evaluation, it was enhanced under guidance of an experienced psychologist and usability expert. It comprised 4 parts:

(i) Part A (posttask assessment) was intended to be filled in directly after execution of each task, separately for each task. It comprised 6 questions.

(ii) Part B (usability and acceptance of the QB) had to be filled in after all tasks were completed. It comprised the 13 questions of the SUS with two additional open questions.

(iii) Part C (suitability of the training) also had to be filled in after all tasks were completed. It comprised 9 questions.

(iv) The questionnaire was complemented by Part D (background information) to collect demographic information. It comprised 10 questions.

A dedicated section in the questionnaire was created for the testers to add their screenshots into the survey.

A complete version of the questionnaire is available as additional file (see Supplementary Material available online at http://dx.doi.org/10.1155/2015/801436).

The evaluation was performed on the EHR4CR QB, accessible through the Internet. The URL to the EHR4CR QB was provided by email.

2.4. Study Flow. This evaluation was conducted across five countries (France, Germany, UK, Spain, and Switzerland) and performed at the usual workplace of the participants to keep a familiar environment and allow them to focus on the EHR4CR QB and assess the system without external influence.

Table 1: Queries construction.

	Query 1		Query 2		Query 3	
	Criterion	Temporal constraints	Criterion	Temporal constraints	Criterion	Temporal constraints
Inclusion criteria						
Gender	Female	—	—	—	—	—
Age	>50 years	—	>18 years	—	>18 years	—
Diagnosis	—	—	Non-insulin-dependent diabetes mellitus	—	Heart failure	At most 3 years before the query
Lab values	—	—	Body mass index $25 < X < 40$	—	Left ventricular ejection fraction <40%	At most 14 months before the query
	—	—	Haemoglobin A1c > 7,5%	—	Systolic blood pressure >2,0 mmHg	2 times separated with at least 2 months in between
Exclusion criteria						
Diagnosis	—	—	Acute myocardial infarction	—	Cardiomyopathy in the puerperium	Between 0 and 5 months before the heart failure
	—	—	—	—	Acute myocardial infarction	Between 5 and 30 months before now
	—	—	—	—	Percutaneous coronary intervention	Between 5 and 30 months before now
	—	—	—		Operation on heart	Between 5 and 30 months before now
Treatment	—	—	Using insulin and analogues	—	Vasodilators used in cardiac diseases	—
	—	—	—	—	Phosphodiesterase inhibitors	—
	—	—	—	—	Cardiac stimulants	—

This table shows criteria composing each query. Users had to construct queries following this pattern in order to find the number of patients corresponding to the set of criteria.

The evaluation occurred within a one-week period (from December 1 to December 5, 2014). At the beginning of the evaluation, anonymous IDs were randomly assigned to the testers in order to preserve their privacy. Another email was sent out to the testers containing the training material. The EHR4CR QB was made accessible at the same time, and anonymized login credentials were provided. The testers were asked to conduct the self-teaching for about 30 minutes on "how to use the EHR4CR QB" with the instruction manual and the demonstration video. They first had to read the instruction manual to get the necessary level of knowledge before starting to use the EHR4CR QB. Following this, they had to watch the 8-minute demonstration video which was a complement to illustrate the purpose of the manual.

All users then performed platform testing following the same test instructions through three predefined tasks for about one hour and a half. Each task consisted in building a query (a set of inclusion and exclusion criteria) and then running the query against endpoints located at different partner hospitals. The aim was to retrieve patient counts corresponding to the predefined set of criteria. The queries were designed to increase the difficulty in a progressive way in order to capture all functionality of the system (see Table 1). Thus, the first query contained only two criteria to construct (gender + age). The purpose here was to familiarize testers with the engine, familiarizing them with basic steps as an introduction. The second query was more representative of what experts face in early stages of protocol design. Its construction was based on real study design queries and constructed by feasibility experts from within the EHR4CR project. The third query was designed to explore all functionalities of the system as the user had to use different temporal constraints and find several inclusion and exclusion criteria in the terminology engine (see Table 1).

2.5. Data Analysis. Based on the responses to the open-ended questions, categories were defined and the responses assigned accordingly. Usability issues mentioned in open-ended questions of questionnaire part A were additionally ranked by a system expert according to their importance. The answers to closed questions of the questionnaire were translated into a numerical scale from 1 (strongly disagree) to 5 (strongly agree). For descriptive analysis, mean scores and standard deviations were calculated. Cases with missing values were deleted listwise. The calculation of the SUS score was based on Brooke's standard scoring method [17]. All values were scaled from 0 to 4, summed up per user, and multiplied by 2.5. This converts the range of possible values from 0 to 100 and allows the values to be compared to a grading scale. Wilcoxon rank sum test was applied for statistically comparing questionnaire results between items. For analyzing if there are groups of relatively homogeneous

answers in the SUS results, a cluster analysis was calculated. At first, Ward's method was used to assess the possible number of clusters. Then, *K* Means Clustering was run with a chosen optimum number to place all the cases. To evaluate whether demographic variables have an influence on the questionnaire results, Pearson correlation was applied. The significance level used for testing was 0.05. All statistics were calculated with the software SPSS 22.0.

2.6. Task Success Analysis. Screenshots with the results from the query construction in ECLECTIC language [18] and the query execution results were manually reviewed and a classification of the task completion and success per user were built, indicating three different levels of success (success, failure, and partial success) based on similar studies [19]. A successful task was defined as follows. The user was able to complete the creation and execution of the query that matched the task goal, and this one contains exactly the same EC as the one built by an EHR4CR QB expert (and from whom the task was defined). A partial success meant that the tester was able to create the query but this one contained two or less minor errors (e.g., wrong use of the temporal constraints) or one severe mistake (e.g., wrong use of the EC). A failure meant that the tester committed more than one medium or two minor mistakes.

3. Results

3.1. Participant Characteristics. 16 managers and specialists with balanced gender and an average work experience of 3 years (SD: 1.680) participated in the second round of the evaluation study. Half of them ($n = 9$) judged their experience with feasibility studies as high; about 80% of the participants ($n = 13$) had not used similar systems in the past. The majority of the participants ($n = 14$) had good and excellent computer skills. The full sample characteristics are presented in Table 2.

Table 2: Sample characteristics.

Variable	*n*	%
Current job group		
Feasibility manager	7	43.75
Data manager	1	6.25
Trial manager	2	12.50
Other (e.g., head of clinical operations, enrolment specialist, clinical operations portfolio manager)	6	37.50
Work experience (years)*	16	3.01 (1.680)
Gender		
Male	7	43.75
Female	8	50.00
(No answer)	1	6.25
Age (years)*	14	43.57 (5.827)
(No answer)	2	
Native language		
English	12	75.00
German/Swiss German	2	12.50
Polish	1	6.25
(No answer)	1	6.25
Difficulties regarding English		
Never, English is my native language	11	66.75
Never, English is not my native language	2	12.50
Rarely	2	12.50
(No answer)	1	6.25
Usage of similar systems in the past		
No	13	81.25
Yes	3	18.75
Experience with feasibility studies		
Little experience	3	18.75
Some experience	4	25.00
Much experience	9	56.25
Computer skills		
Average computer skills	2	12.50
Good computer skills	8	50.00
Excellent computer skills	6	37.50
Knowledge in Boolean algebra		
No knowledge	3	18.75
Little knowledge	4	25.00
Average knowledge	3	18.75
Good knowledge	5	31.25
Excellent knowledge	1	6.25

Characteristics of the participants ($n = 16$). Summarized number and row percentage per category; *for "work experience" and "age" mean and standard deviation were calculated; $n = 16$ participants.

3.2. Questionnaire Results

3.2.1. Perceived Task Difficulty and Satisfaction. Across the three tasks of the study task 1 (mean: 3.94, SD: 0.929) and task 2 (mean: 3.75, SD: 1.000) on average were rated as "somewhat easy"; task 3 was judged as "neutral" (mean: 2.63, SD: 1.088). Overall, participants were satisfied with the ease of completing the tasks (task 1: 3.81, SD: 0.911; task 2: 4.06, SD: 0.575) or "neutral" in this regard (task 3: 2.75, SD: 0.858). Satisfaction with the amount of time it took to complete tasks was "rather high" for task 1 (mean: 3.88, SD: 0.885) and task 2 (mean: 3.75, SD: 0.856) and rated as "neutral" for task 3 (mean: 2.94, SD: 0.680). Likewise, satisfaction with functionality provided when completing the tasks was judged as "rather high" (task 1: 3.69, SD: 0.873; task 2: 3.81, SD: 0.655) or "neutral" (task 3: 2.88, SD: 0.957). Significance testing with Wilcoxon rank sum test revealed that all differences of judgements between tasks 1 and 3, respectively, and tasks 2 and 3 were significant (see Table 3).

The analysis of open-ended questions still identified shortcomings of the EHR4CR QB; for example, there was no ability to execute results for all countries, the sequence of building a query was not clear (systems seemed to require it in reverse), there was a lack of system feedback when saving the query, and specific values of criteria were not directly

Table 3: Perceived task difficulty and satisfaction.

Item	Task 1		Task 2		Task 3		Wilcoxon-Test, p value		
	Mean	SD	Mean	SD	Mean	SD	T1-T2	T1-T3	T2-T3
Task difficulty	3.94	0.929	3.75	1.000	2.63	1.088	0.582	0.006*	0.005*
Satisfaction with the ease of completing the task	3.81	0.911	4.06	0.574	2.75	0.856	0.271	0.007*	0.001*
Satisfaction with the amount of time it took to complete the task	3.88	0.885	3.75	0.856	2.94	0.680	0.755	0.017*	0.005*
Satisfaction with the functionality provided	3.69	0.873	3.81	0.655	2.88	0.957	0.557	0.010*	0.002*

Mean ratings (5-point rating scale), standard deviations, and p values of Wilcoxon-Test, * significant at the $p = 0.05$ level; $n = 16$ participants.

visible because this information required scrolling. Expert review revealed that the majority of these usability issues are important (see Table 4).

3.2.2. Overall Usability, Design, and Comfort. Participants' responses to the SUS are presented in Table 5. The average SUS score was 55.83 (SD: 15.37) "ok" ranging from 22.50 "worst imaginable" to 80.00 "good." Cluster analysis revealed two clusters: cluster 1 ($n = 8$) with a mean SUS score of 67.5 "ok" and cluster 2 ($n = 7$) with a mean SUS score of 42.5 "poor." Further correlation analysis according to Pearson revealed no statistical significant correlations between the SUS score and participant variables like age (0.114, p: 0.687), gender (0.219, p: 0.451), years of job experience (0.248, p: 0.373), experience with feasibility studies (−0.084, p: 0.766), computer skills (0.011, p: 0.969), and knowledge in Boolean algebra (−0.196, p: 0.483). Additionally formulated items for assessing design and comfort showed that participants on average were positive about the design of the interface (mean: 3.56, SD: 0.814), felt comfortable using the QB in English (mean: 4.38, SD: 0.719), and felt comfortable with the way of building a query (mean: 3.50, SD: 0.730).

In the question regarding what participants appreciated most about the QB they named (a) user-friendliness ($n = 9$), primarily the very intuitive drag and drop interface, the user-friendly terminology, and ease of learning and the layout and (b) functionality of the QB ($n = 5$). With regard to the functionality especially simplified search operators across medical terminology, timeline options for diagnoses, possibility to edit queries, predictive searching capability when finding terms to be included, and data that can be obtained were assessed positively.

Room for improvement may focus on enhancing the user-friendliness by providing more icons (the system is seen as "program" based which can put off nontechnical people) ($n = 1$) and enhancing the user-friendliness of terms ($n = 1$). Furthermore, participants suggested extensively revising the logic of the sequence of adding clinical parameters and timeline parameters ($n = 3$). The options to define time ranges and occurrences should also be reworked ($n = 3$). Additionally, functions to multiselect terminologies and to link two search criteria (because some of them are interdependent upon each other) should be available ($n = 1$). The search items should be provided in a "medical sort" (which most probably was intended to denote "medical sorting order"), not alphabetically ($n = 1$). In addition, the search function should be improved to find the search terms, for example, by a phonetic search, and different ways of searching should be offered ($n = 2$). Further, participants noted that a confirmation notification after updating information in the text field would be helpful ($n = 1$). Other comments were that the constraints can be confusing (when and how to apply them) ($n = 1$) and that disruption can occur if specific content shall be copied ($n = 1$). Besides, the reference number of each criterion should be available for reuse in subsequent inclusion/exclusion criteria ($n = 1$) and it should be referred to criteria within the query rather against the parent search terminology ($n = 1$). Shortcuts ($n = 1$) and a help function were also suggested ($n = 2$).

3.2.3. Quality of Training. Overall, participants were satisfied with the training (mean: 3.53, SD: 0.640) and agreed that the topics were relevant for the tasks (mean: 4.20, SD: 0.414). Furthermore, they stated that the training material was helpful (mean: 4.13, SD: 0.352) and that the content was well organized and easy to follow (mean: 3.93, SD: 0.640). Participants also were positive about the speed of the training video (mean: 3.64, SD: 0.842) and the time allotted for the training (mean: 3.54, SD: 0.877). However, they mostly did not agree to have enough information available (mean: 3.27, SD: 1.033). Regarding the usefulness of the training experience for work, participants were rather neutral (mean: 3.40, SD: 0.737) (see Table 6). Pearson correlation analysis revealed no statistical significant relationships between overall training satisfaction and participants' variables (age: −0.010, p: 0.972; gender: 0.230, p: 0.428; years of job experience: 0.073, p: 0.795; experience with feasibility studies: −0.228, p: 0.414; computer skills: 0.066, p: 0.815; and knowledge in Boolean algebra: 0.273, p: 0.324).

Asked for recommendations to improve the training, participants named (a) optimization of the video with respect to higher resolution, audio instructions, text cues, and reduction of video speed ($n = 7$), (b) provision of clearer instructions (e.g., on the sequencing of questions and how to deal with time occurrences) and more specific details about the queries (e.g., it was not clear what is meant by "first" and "last" in the EHRs in this context) ($n = 7$), (c) improvement of the terminology for sections and provision of more information regarding the terms ($n = 2$), and (d) language enhancements ($n = 3$).

3.3. Task Success. The results of the task success analysis (see Table 7) show that testers were able to correctly complete the creation and execution of queries 1 and 2 in ten out of thirteen cases, whereas four out of twelve of the testers could successfully complete query number 3. Two of the

Table 4: List of usability issues encountered by participants.

Task	Missing functionalities	User number	Expert review
Task 1	Criteria of >49 years were selected but appear as ≥49 years	User 01	Not important; mistake in specification of query not tool
	No ability to execute results for all countries, only for UK/no response when clicking on all countries	User 19	Medium importance; probably a problem with available sites not with the tool
	The query in eclectic format did not show up and looked similar to screen shot in training manual	User 06	Low importance; feature only used for testing probably be removed for "real world" version of tool
Task 2	Than & less selections appear transformed into more & less than OR EQUAL to	User 01	Not important; mistake in specification of query not tool
Task 3	The sequence of building the query is not clear; system seems to require it in reverse (i.e., the parameters of time to be entered before the diagnosis)	User 18, user 19	Important; comment on usability though unspecific
	Entering exclusion criteria (e.g., 3.3.4 EC02) is cumbersome	User 06	Important; comment on usability though unspecific
	No visible option how to add a range of 5–30 months; the range always began at 0 months	User 01	Medium importance; option is there when user selects "between" rather than "more than" or "less than," user interface issue, or poor documentation
	No way to clear just one component from the query; "clear" clears all components/if you want to change particular part of the inclusion or exclusion criteria, you have to delete the whole; it would be better to delete parts	User 06, user 21	Medium/low; true but the individual inclusion sections are never hugely complex so deleting all is not too bad
	The "before now" button did not work several times	User 19	Important; was not seen this reproduced though
	The run function and eclectic format were not possible; computer crashed when running the query or doing it in eclectic format/"does not compute" message appeared, when trying to generate the eclectic format	User 21, user 01	Important; a "crash" reproduced elsewhere was not seen
	System feedback was that query had been saved, but it does not appear to have been	User 01	Important; true in terms of lack of feedback, but it is always saved
	If you want to check a specific value of a criterion (e.g., if left ventricular ejection fraction was correctly entered and you want to check it later) you are not able to see it by clicking on the symbols	User 21	Important; this information appears at the bottom of the screen and not where user would originally see it and may need to scroll, user interface issue

Responses to the open-ended question "What function or feature do you miss for this task?," and expert review of usability issues; $n = 16$ participants.

Table 5: Results of the System Usability Scale (SUS).

SUS item	N (valid)	Mean	SD
I think that I would like to use the Query Builder frequently	16	3.63	0.885
I [did not find] the Query Builder unnecessarily complex*	16	3.06	0.929
I thought the Query Builder was easy to use	16	3.38	0.719
I think that I [would not] need assistance to be able to use the Query Builder*	16	2.94	0.998
I found the various functions in the Query Builder were well integrated	15	3.07	0.961
I [did not think] there was too much inconsistency in the Query Builder*	15	3.33	1.047
I would imagine that most people would learn to use the Query Builder very quickly	16	3.25	1.000
I [did not find] the Query Builder very cumbersome to use*	16	3.19	0.834
I felt very confident using the Query Builder	16	3.06	0.854
I [did not need] to learn a lot of things before I could get going with the Query Builder*	16	3.00	1.033
Overall SUS score	**15**	**55.86**	**15.37**

Mean rating (5-point scale from 1 "strongly disagree" to 5 "strongly agree"), standard deviations, and overall SUS score. Items marked with an asterisk (*) were reverse coded; $n = 16$ participants.

Table 6: Quality of the training.

Items	N (valid)	Mean	SD
The topics covered by the training were relevant for the tasks	15	4.20	0.414
The time allotted for the training was sufficient	13	3.54	0.877
The content of the training was well organized and easy to follow	15	3.93	0.458
The materials distributed were helpful	15	4.13	0.352
The speed of the training video was appropriate	14	3.64	0.842
The amount of information was sufficient for solving the tasks	15	3.27	1.033
This training experience will be useful in my work	15	3.40	0.737
Overall, I am satisfied with the training	15	3.53	0.640

Mean ratings (5-point scale from 1 "strongly disagree" to 5 "strongly agree") and standard deviations; $n = 16$ participants.

Table 7: Task success.

User ID	Task 1	Task 2	Task 3
User 1	S	S	F
User 2	P	P	
User 3	S	S	F
User 4	F	S	P
User 5		S	F
User 6	S		F
User 7	S	S	S
User 8	S	S	P
User 9	S	S	F
User 10	S	S	S
User 11	S	S	S
User 12	S	P	P
User 13	S	S	S
User 14	F	F	

S: success is given when the whole completion of the task is successful. P: partial success is given when the user commits no more than a severe mistake (wrong use of the EC) or no more than two minor mistakes (wrong use of the temporal constraints). F: failure is given when the user commits more than one severe mistake or more than two minor mistakes.

testers did not share the screenshots containing the results and other four either did not share one of the queries or the screenshots were insufficient to determine the success of the task completion.

4. Discussion

The system users stated that the platform was easy to use and that they were able to perform the tasks for which it was designed with the provided amount of training. There were many positive comments towards functionality and usability. However, the SUS of nearly 56, in the threshold of an "OK" result, suggests that there is still room for improvement. This is also reflected by the free text comments that suggested modifications to the platform usability. According to the feedback given after the completion of the tasks, it seems that for simple and normal queries the system is usable, but for complex ones the users have difficulties (see Tables 3 and 7). It cannot be concluded whether this is due to system deficiencies or insufficient training.

4.1. Strengths and Weaknesses of Study. To assure a robust and reliable methodology, this study was preceded by a pretest to assure the technical system functionality and the appropriateness of the methodology.

The different levels of query complexity were designed for a test environment. Only the second query reflected a real feasibility query. The third query was especially designed to test different functionalities and the temporal constraints. This type of query is not likely to be used in a real world scenario. Interestingly this query had not only the highest error rate but also the highest difficulty and lowest satisfaction among the user ratings. The free text comments showed that the provided training was not sufficient for those kinds of queries. It might be possible that the SUS was biased by the difficulty and the inability to successfully complete the task, as the users were asked to complete the SUS questionnaire immediately after finishing the third query.

An alternative evaluation approach would have been to make use of the Thinking Aloud method instead of (or complementing) the SUS, as, for example, in [20]. Since the study was executed at the participant's workplace, this method seemed inappropriate, though. Furthermore, using a standardized and established method that produces a single overall score like the SUS makes the outcome comparable to possible future studies that examine a similar matter.

The test setting was not absolutely the same for all participants since the study was executed at their workplace. Unrecorded distractions might have occurred. However, this was allowed since it reflected a realistic scenario rather than a laboratory setting.

The questionnaire was provided in English only. In [21], Finstad demonstrated that the vocabulary used by the SUS might be hard to understand by nonnative speakers. However, since 75% of the participants were native English speakers (Table 2), the probability of a language induced bias can be considered to be rather low.

The relatively low number of participants ($n = 16$) might be considered a methodological weakness. However, the basic population of suitable domain experts with no knowledge of the platform was already quite low beforehand. Tullis and Stetson [22] showed that a sample size of about 12 participants yields good results for the SUS. Therefore, 16 participants can be considered sufficient. However, the effect of expertise must be taken into consideration with respect to usability

testing in general and the SUS in particular. Experienced users in a given domain tend to provide a slightly higher, more favourable SUS score than users with either no or limited experience [23]. The demographic analysis shows that about half of the participants assessed themselves to have much experience with feasibility studies (see Table 2). This might have tampered the SUS score.

4.2. Relation to Other Studies. The technical query model that is used to collect the patient cohorts from the distributed data sources [9] and the possibilities and requirements for an actual use of the EHR4CR platform [24] have already been evaluated in earlier studies.

The usability of patient cohort identification systems for the purpose of clinical trial feasibility assessment, however, has only been examined for a few isolated solutions so far. In 2005 [25], the evaluation of a clinical trial alert system that triggered reminders whenever patient data met EC during routine visits is described. A survey comprising 14 questions was used for that study; no standardized method was used and no score was calculated. The evaluation of another site-specific tool named "ASAP" (Advanced Screening for Active Protocols) from the Ohio State University Medical Center was published in 2012 [20]. That study is based upon Thinking Aloud protocols and a survey of 10 questions. The users of the ASAP system were asked to rate the ease of use and the perceived usefulness of the tool for the user's clinical environment on a Likert scale of 1 to 5. Additionally, the users were asked if the tool would be useful for screening patients based on their experience during the usability test. Again, no standardized usability testing and no score calculation took place.

A project with a similar scope like EHR4CR and the FARSITE evaluated the technical results but not the usability [8]. Another project with a complexity comparable to EHR4CR, but with a different focus, is the Cancer Translational Research Informatics Platform (caTRIP) as part of caBIG (Cancer Biomedical Informatics Grid), which allows querying across a number of data services, joining common data elements, and viewing the results. It provides the user with the ability to construct, execute, and share distributed queries in a graphical environment. The user interface is claimed to be user-friendly, but the proof is not provided [26].

Finally, an evaluation of the i2b2 user interface needs to be mentioned, since i2b2 provides a comparable functionality and a comparable query assembling paradigm like the EHR4CR QB. The abstract of that study [27] claims that the usability of i2b2 was evaluated, but it actually rather evaluated the applicability (i.e., if it can be used for a given scenario) than the usability.

In summary it can be stated that, to the authors' knowledge, this investigation is the most systematic usability evaluation, including a usability score, of a cohort identification system for CTs so far.

4.3. Meaning and Generalizability. As a qualitative rather than quantitative study, questions of the generalizability of the results rest on the extent to which the selected users can be seen as typical of the eventual desired population of users for the platform. The selection of users for this study came from within the EHR4CR project, meaning that this selection is from precisely the target population of users of the tool. This would indicate that the composition of the study would carry a high degree of situational representativeness. However, due to the qualitative nature of the results it is difficult to justify with certainty the applicability of the results to different sets of users, possibly from different countries and different working environments.

In terms of the characteristics of the study population, half of the users judged their current experience with feasibility studies as "high." It could be expected that users of the system, when deployed in a real world scenario, would fall more into this category than nonexpert users as such a system would most likely be deployed to complement existing feasibility tools or practices. Given the relatively low number of participants in the study it was not possible to derive any statistically valid results from a comparison of expert and nonexpert users, where perhaps such an analysis of the responses split along these lines would have yielded differences in the subject's view of the system.

The study asked participants to construct three feasibility queries of varying complexity. Of these, the first focused only on the most basic features of the QB portion of the platform whilst the third was a catch-all for the full range of advanced functionality available. Only the second, which was based on the transformation of a real world country feasibility study criteria by experts, could be seen to reflect more accurately the type of criteria that the tool would be used to construct in real world use cases. As such the results of the study, which were derived from feedback from users based on carrying out all three tasks (easy to complex), may not generalize to real world use cases predominately reflected by the type of query.

4.4. Future Work/Questions. The EHR4CR project team may consider enhancing the current system utilizing the feedback from the testers presented in this paper. In a future study it should be tested whether users have fewer difficulties with temporal constraints and very complex queries if more specific training is provided to them.

5. Conclusions

The user satisfaction of the EHR4CR QB was successfully evaluated with a positive result in a real world, multinational setting. Functionalities of time constraints need to be revisited as they are often part of clinical trials EC. It has been proven that, with a relatively small amount of training, users are able to correctly create and execute simple feasibility queries in the EHR4CR QB. Besides, this evaluation provides a list of features and modifications that such systems should comply to.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

Authors' Contribution

Aurèle N'Dja and Iñaki Soto-Rey managed the evaluation team, collected the data, and wrote the paper. James Cunningham developed the training material, was part of the peer group, and helped to draft the paper. Axel Newe created the questionnaire, was part of the peer group, and helped to draft the paper. Benjamin Trinczek provided technical support, was part of the peer group, and helped to draft the paper. Caroline Lafitte participated in a pretest, provided user advice, and helped to draft the paper. Brita Sedlmayr and Fleur Fritz analysed and discussed the results, supervised the methodological approach, and helped to draft the paper. All authors read and approved the final paper. Iñaki Soto-Rey and Aurèle N'Dja (as leading authors) as well as Brita Sedlmayr and Fleur Fritz (as senior authors) contributed equally to this work.

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Research Article

Contribution of Electronic Medical Records to the Management of Rare Diseases

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Purpose. Electronic health record systems provide great opportunity to study most diseases. Objective of this study was to determine whether electronic medical records (EMR) in ophthalmology contribute to management of rare eye diseases, isolated or in syndromes. Study was designed to identify and collect patients' data with ophthalmology-specific EMR. *Methods.* Ophthalmology-specific EMR software (Softalmo software Corilus) was used to acquire ophthalmological ocular consultation data from patients with five rare eye diseases. The rare eye diseases and data were selected and collected regarding expertise of eye center. *Results.* A total of 135,206 outpatient consultations were performed between 2011 and 2014 in our medical center specialized in rare eye diseases. The search software identified 29 congenital aniridia, 6 Axenfeld/Rieger syndrome, 11 BEPS, 3 Nanophthalmos, and 3 Rubinstein-Taybi syndrome. *Discussion.* EMR provides advantages for medical care. The use of ophthalmology-specific EMR is reliable and can contribute to a comprehensive ocular visual phenotype useful for clinical research. *Conclusion.* Routinely EMR acquired with specific software dedicated to ophthalmology provides sufficient detail for rare diseases. These software-collected data appear useful for creating patient cohorts and recording ocular examination, avoiding the time-consuming analysis of paper records and investigation, in a University Hospital linked to a National Reference Rare Center Disease.

1. Introduction

Eye health and vision-related conditions related to rare diseases constitute a critical public health issue in countries such as France. The French Government certifies National Reference Centers on rare disease for specific diseases in University Medical Centers in order to improve the quality of health care and support of patients with more than 7,000 listed rare diseases. The concerted efforts by clinicians and scientists interested in these diseases to collect families and refine phenotypic delineation over several decades have led to the discovery of rare genetic diseases. An Italian study of rare diseases estimated the overall raw prevalence at 33.09 per 10,000 inhabitants. Ocular disorders are an example of the most common rare diseases with a prevalence of 4.47 per 10,000 inhabitants [1]. There is an ever-growing need for identification and surveillance of rare eye disease because vision impairment and blindness are major public health problems [2]. Health care systems are increasingly adopting robust electronic health record systems that can not only improve health care but also contain a wide range of data derived from the patient's examination [3]. In ophthalmology, a wide range of data is acquired from patients, requiring the use of specific electronic medical records. However, significant information remains locked in paper text documents, including clinical notes and certain categories of test results. In addition, rare diseases may take a considerable time to accrue in these datasets. A combination of simple free-text

searches may be sufficient to obtain informative data from the electronic medical record system for relatively rare cases. A model that is gaining acceptance is clinical innovation based on phenotype information. The information is provided by electronic health records likewise on proposed new therapeutics for patients with rare disease. Typical clinical research is based on purpose-built cohorts or observational studies. Electronic health records are primarily designed to support clinical care, billing, and increasingly other functions such as improvement of quality of life. The present study was designed to determine whether ophthalmology-specific electronic medical records are useful for the management of rare eye diseases or rare syndromes with eye involvement.

2. Methods

This study was designed to identify and collect data from patients with specific rare eye diseases, registered with ophthalmology-specific electronic medical records at an eye center. Five rare diseases were selected on the basis of their rarity and the center's particular expertise. The five diseases selected for this study were congenital aniridia, Axenfeld/Rieger syndrome, Blepharophimosis-Epicanthus-Ptosis Syndrome (BEPS), Nanophthalmos, and Rubinstein-Taybi syndrome.

2.1. Patient Data. The study was carried out in the Department of Ophthalmology at University Medical Center of Amiens. The names and data of patients with the five selected rare eye diseases were collected. The patients were seen at the Rare Eye Diseases Reference Center in Amiens linked to the National Reference Rare Eye Disease Center in Paris from 1 January 2011 to 31 December 2014. All patients attending an outpatient visit and patients undergoing inpatient or outpatient surgery were included.

2.2. Electronic Medical Records. An ophthalmology-specific electronic medical record software was installed in the DX Care institutional electronic health records at University Medical Center of Amiens in January 2010. A descriptive, longitudinal record is created for each patient to describe the events at each meeting with the patient. The record describes all visits attended by the patient, case histories, diagnoses, medications, medical and surgical procedures, tests, and investigation results. The main types of information available from EMRs are laboratory results and vital signs, provider documentation, documentation from clinical ocular examinations and tests, medication records, and tests' results such as visual field, corneal OCT, corneal topography, pachymetry, tear osmolarity, macular OCT, and electrophysiology. Each user is assigned a personal user name and password. The system ensures a high level of security and is accessible to clinicians working at the center including residents and fellows who enter patient data as well as the center's health care providers.

2.3. Methods. During the period from 1 January 2011 to 31 December 2014, patients were examined at the University Medical Center of Amiens and their data were recorded in the specific electronic medical record (software for ophthalmologists Softalmo Corilus, France). Physicians, nurses, and medical secretaries log onto the software with an individual login and password or an external professional card reader. The software comprises the patient's administrative data and the patient's detailed ocular examination. The EMR ocular examination includes the following fields: purpose of the consultation, history of symptoms and clinical signs, treatment, allergy, patient's medical history, family medical history, ocular motility, lids and lacrimal drainage, visual acuity (noncorrected, corrected, with cycloplegia, and optical correction), refraction, slit lamp examination, intraocular pressure, fundus examination, diagnosis, conclusion, orthoptic examination, and remarks (Figure 1). The electronic medical record is also linked to all of the new ocular investigations, such as IOL Master A scan, pachymetry, anterior segment OCT, posterior segment OCT, all types of corneal topography, all types of visual field technologies, electrophysiology, fundus photography, and angiography. Five specific rare eye diseases were studied in the patients' files. "Ophtalmo Query" from Softalmo (Corilus) computer search software was used to identify all terms for each rare disease in all text fields of the ocular electronic medical record.

Table 1: Rare disease EMR research.

Rare diseases	Patients of active file	Number of visits (2011–2014)
Aniridia	29	61
Axenfeld-Rieger syndrome	5	42
BEPS	11	33
Nanophthalmos	3	7
Rubinstein-Taybi syndrome	3	10

3. Results

From 1 January 2011 to 31 December 2014, 135,206 patients attending a consultation at University Medical Center of Amiens and 16,039 patients undergoing inpatient or outpatient surgery were included using ophthalmology-specific electronic medical records Softalmo (Corilus). The five rare eye diseases were identified from the files of outpatients of the center by using the search function of the software (Ophtalmo Query). The results are reported in Table 1. The frequency of visits for each rare disease is reported in Table 1. For each rare disease selected with patients' names corresponding patient's data are collected. All visual investigations performed were available at the same time with the ophthalmology-specific EMR. The search software identified 29 patients with congenital aniridia, 6 patients with Axenfeld/Rieger syndrome, 11 patients with Blepharophimosis-Epicanthus-Ptosis Syndrome (BEPS), 3 patients with Nanophthalmos, and 3 patients with Rubinstein-Taybi syndrome. The frequency of the visits was different for each rare disease. In 4 years, aniridic patients had a mean of 2.1 visits, Axenfeld/Rieger syndrome patients had a mean of 8.4 visits, BEPS patients had a mean of 3 visits, Nanophthalmos patients had a mean of 2.3

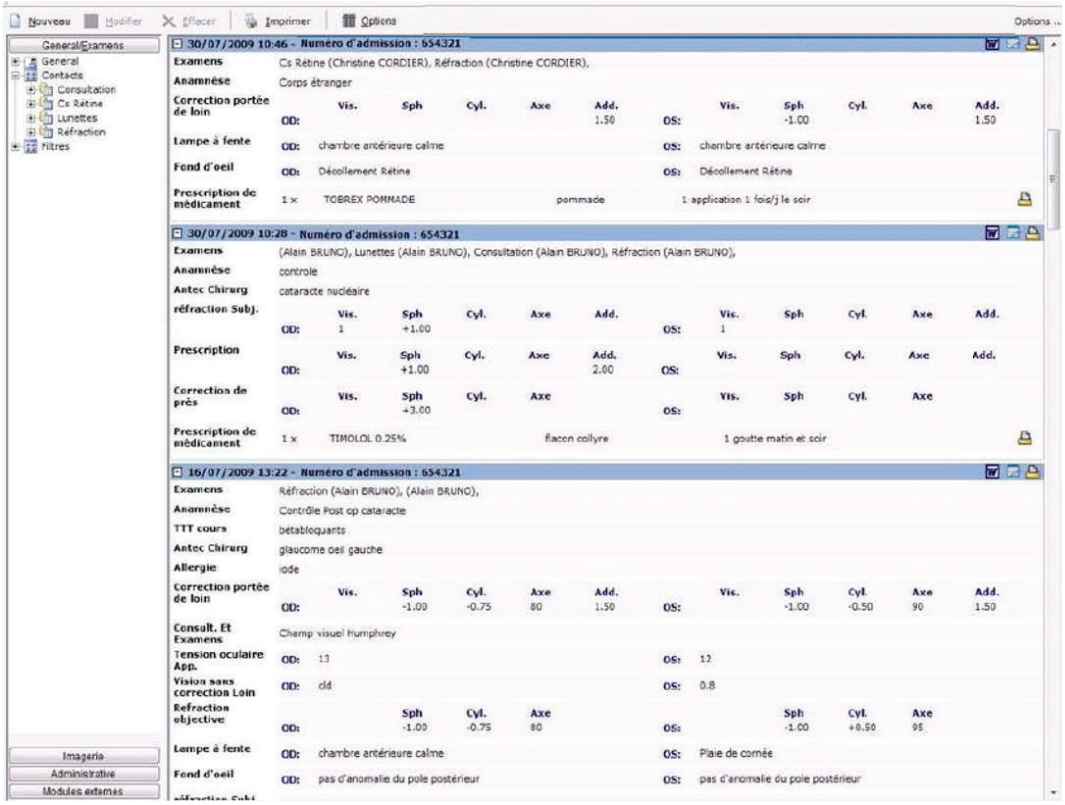

Figure 1: Softalmo software, ophthalmological medical record main page.

visits, and Rubinstein-Taybi syndrome patients had a mean of 3.3 visits. The EMRs for each of these patients were reviewed to confirm the accuracy of the diagnosis. A combination of simple free-text searches followed by manual chart review may be sufficient for relatively rare case reports.

4. Discussion

Electronic medical records provide a number of advantages in terms of medical care, including decreased paperwork, improved administrative efficiency, reduction of time-consuming medical record data collection, and decreased data processing burden [4]. The use of nonspecialized electronic medical records can present serious clinical drawbacks for eye care providers, as the used system may not be adequate documentation of ophthalmological examinations and care. Typically, patient questionnaires and/or analysis of research staff are used to determine the patient's phenotypic traits. These very costly and time-consuming models are common and represent only a specific point in time. Our study demonstrated that the ophthalmology-specific EMR system used in the Ophthalmology Department of University Medical Center provides accessible and reliable information. The ophthalmic EMR is specific and can contain ocular information not easy to include in a general EMR. This study emphasizes the value of EMR for data collection in rare eye diseases. The use of studies of EMR for data collection in rare eye diseases will be done with approval by the Human Research Ethics Committees. Specific and adapted ophthalmological electronic medical record software can provide real-time data including all ocular tests and ophthalmological investigations [5]. This automated data extraction is much less time-consuming than traditional chart-based reviews of medical records [6]. In addition, electronic medical records data entered by care providers during the medical care process are objective, whereas survey data based on patients' self-reports are not objective. A key advantage of ophthalmology-specific EMRs is that they allow collection of phenotype information as a by-product of routine health care. Moreover, this data collection becomes more extensive with time and is continually refined as new information confirms or excludes a diagnosis in a given individual. Data concerning disease, response to treatment, and laboratory test data are collected during the patient's lifetime. Aggregation of this information can allow larger sample sizes for certain rare diseases and is particularly useful for patients with a rare disease [7]. EMR requires a significant institutional investment and ongoing financial, ethical, and logistical support to operate effectively. Even the implementation of an electronic medical record system that meets these particular needs may lack the charting function required to document eye examinations and care. Implementation of an EMR system is also likely to involve an initial loss of income due to the time devoted by health care providers to installing, learning, and personalizing the system. Funding is also required for staff training and acquiring resources to use and maintain the system [1]. However, eye care professionals need to be involved in the EMR design process in order to

ensure effective workflow integration and the inclusion of EMR components specific to eye care. Finally, integration of the system into daily care appears much easier under these conditions. EMR is not yet universally available but provides major advantages for equipped centers for the management of rare diseases. The frequency of the visits of patients with rare eye disease or syndrome with eye involvement must be analysed for improved health management or customized patient pathways for rare eye diseases. EMRs can help improve eye health in rare diseases by analyzing data derived from patient cohorts. EMRs could possibly facilitate information sharing locally and in the department and with national university medical centers and national rare disease centers once this type of data exchange is supported.

5. Conclusion

Finding information on rare diseases is a data mining problem due to the small number of patients and the complexity of the disease. Processing a large number of records requires an automated extraction and classification process. In conclusion, our study demonstrated the reliable information on targeted rare diseases provided by the ophthalmology-specific EMR system. A cohort of patients can be constructed for each rare disease, which can therefore be useful for rare disease public health centers. The collection of accurate patient data constitutes a major challenge. The value of data for a given rare disease of interest is therefore essential to improve clinical research. The use of specific EMR data may allow improved surveillance of rare diseases, including surveillance of eye health and vision-related conditions. The sharing of data with all centers caring for patients with a rare disease will ultimately support clinical research and innovation.

Conflict of Interests

The authors declare that there is no conflict of interests regarding the publication of this paper.

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