# The HL7 Common Clinical Registry Framework: a domain analysis model for clinical registries

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## Executive Summary

A clinical registry is an organized system that uses observational study methods to collect uniform data (clinical and other) to evaluate specified outcomes for a population defined by a particular disease, condition, or exposure, and that serves one or more pre-determined scientific, clinical, or policy purposes. (1) Clinical registries can collect data from many sources, including but not limited to EHRs, clinical information systems (CIS), patient-facing and other applications. Some data are also directly entered into registries by clinicians through manual chart abstraction into a secure web interface, and by patients through registry patient portals. Registries provide structured, verified, validated specific data needed to measure health care performance across a wide range of clinical domains, geographic areas and patient populations over varying periods of time for a variety of purposes. The need to populate registries with data of this type from multiple disparate source data systems is driving a need for improved interoperability between registries and other CIS.

In health care, interoperability describes the extent to which different health IT systems can exchange data and interpret the information shared in the data. Interoperability occurs at different levels; foundational or syntactic interoperability allows for the successful transfer of a data payload between two systems, without regard for the receiving system’s ability to interpret the information contained in the transferred data. A semantic level of interoperability implies that the meaning of the information is properly preserved in the transfer. A final level is functional or process interoperability, in which the connectivity between two systems not only allows for the successful transfer of information with meaning intact, but also directly supports the clinical or operational processes that the interoperability serves. (2)

Sources of health data for registries include direct entry into the registry, EHRs, CIS such as radiology PACS and other health IT. These sources provide clinical and administrative data from clinicians and provider organizations throughout the health care delivery system. Although much routine health data are captured in EHRs and other health IT, specific, structured data that facilitate benchmarking, quality improvement, payment, clinical research and other uses are often lacking in these source data systems. Clinical registries close this gap by collecting highly structured data, clinical and other, that are standardized within the registry across all of the clinicians and provider organizations participating in the registry. Although some registry data are collected explicitly as a result of clinician participation in registry programs, an increasing percentage of these data are automatically extracted from EHRs and other health IT (PCPI research survey data; unreferenced).

As registries collect data from real-world patient populations in a common format, often across multiple provider organizations and over varying periods of time, data from multiple source data systems must be captured in the registry in a way that preserves the meaning of the information transferred. Today, this requires that data either be manually entered into or converted into structured formats, which is facilitated by the use of data dictionaries, common data elements, or in some cases data standards, into source data systems or through the creation and use of custom data system integrations. It is anticipated that in the future, natural language processing (NLP) and similar technologies will further enhance the ability to utilize unstructured free-text data combined from source data systems together as unified data sets. Although NLP does not eliminate the need for data standards *per se*, until such time as NLP may ameliorate the need for discreet formats to support structured data capture, additional standardization is needed. To that end, Health Level Seven International (HL7) and PCPI are collaborating to support the development of standards, in the form of a domain analysis model for a general clinical registry that will support the interoperability of registries with other health information systems.

Domain analysis models (DAMs) describe the concepts and relationships of a given domain, which is a specified sphere of activity or knowledge. They identify the data elements used in the domain, activities and uses (or use cases), as well as the clinical setting, through the use of story scenarios and a supporting conceptual model that specifies the relationship of the data elements to each other. In this white paper, the authors describe a DAM for a general clinical registry, justify its need, and demonstrate how its use can enhance the sharing of information across clinical registries and other health IT to improve care quality and patient health outcomes.

## Introduction

Clinicians provide care for their patients and document in EHRs, registries and other health IT. The source data come from direct clinician entry i.e., into the EHR, and from other health IT that automatically input specialized clinical information such as lab tests and radiology imaging examinations into the EHR. Data are also captured into registries through automated extraction from EHRs or via direct entry from manual chart abstraction. Any data that are not entered manually into a registry, such as through a secure web interface, must be extracted from source data systems or data warehouses, transmitted to the registry, verified, validated and if needed formatted for entry into the registry database. Through a combination of analytic software and expert monitoring, registry data are analyzed and then used for any number of primary and secondary uses. Typical primary uses of registry data include the provisioning of feedback to participating clinicians in the form of performance reports, which inform them about their performance relative to their peers or other benchmarks or performance standards. Information contained within registry feedback reports can then become the basis for quality improvement projects or programs. Additional uses of registry data include the reporting of performance measure results to public and private payers to support value-based payment models, benchmarking, clinical research and education.

A fundamental difference between registries and other CIS is that registries are designed for narrow clinical purposes rather than for general data collection, administrative and legal compliance purposes and are generally secondary users of the data collected. Working back from the specific purposes envisioned for a new registry, data elements, formats and structures are identified and prioritized according to their contribution to the strength of the registry dataset and their feasibility to collect. Strict procedures (manual or automated) are designed to ensure that data are mapped or entered in the same format, according to the same definitions, across multiple participating clinicians, source data systems, care settings and organizations. It is in this way that clinical registries facilitate the capture of verified, valid, trustworthy data on real-world patient populations, from which performance can be measured and reported on a national level.

Registries are designed to facilitate the harmonization of captured data from multiple source data systems into a unified view of care in the registry’s domain. Verification and validation of data occur both on input and afterwards on an ongoing basis. As in other CIS, data are analyzed and then used for a variety of purposes. Registry information may sometimes also be incorporated back into clinical workflows, either via registry software that clinicians and even patients interact directly with, or as a feedback mechanism into EHRs or other workflow-facilitating CIS.

Computing systems including health IT currently have a limited ability to make inferences and apply nuance to the capture, storage and use of data. In short, they still must be told exactly what to do and precisely what the data mean. If this is not done, the result may be random or nonsensical. The process of specifying information as precisely as possible begins with data standards, and data standards work starts with standard data elements and ontologies. Standard data elements are terms or concepts, their definitions and allowable values used in a domain, in this case clinical medicine and health care practice. In computing, ontologies are formal representations of entities or concepts, such as patients, physicians, equipment or treatment, and relationships that apply in a domain. Data Elements and ontology data standards allow clinical concepts to be constructed hierarchically e.g., SNOMED CT and LOINC®. More complex clinical concepts, such as patient history, vital signs, procedures or courses of treatment, benefit from standardized methods of defining and structuring data elements in groups to sufficiently describe these concepts in a single instance such as a patient visit or encounter record.

One standard that supports these activities is the HL7 Clinical Document Architecture (CDA). In addition to these clinical standards are services standards. These are more general technical standards, not necessarily unique to health care, that allow instances of these data structures to be organized for transport on various communication networks, transported between systems and correctly interpreted by the receiving systems. (3) The CDA is a standard that may help address the challenges of data exchange between registries and source data systems. Registries heavily rely on the exchange of data between various EHRs, CIS and manual data submission, which is driven by custom requirements provide by the registry. Providers that submit to multiple registries have custom applications and scripts for each registry they support. Common data exchange formats across registries may reduce the need for multiple customizations and programming. To facilitate manual capture or exchange directly from a EHR or CIS, common or standard functions may also facilitate smoother data exchange and reduce the layers of programming for each registry. Functional standards may help with facilitating collection of registry information during a patient encounter through existing EHR or other CIS, as well as the exchange of data between registries. Exchange standards can facilitate the data exchange mechanisms to reduce the need of customized programming for each separate registry.

The achievement of semantic interoperability between registries and other health IT requires the adoption and use of data standards, exchange and system functional standards across this conceptual spectrum. Various factors have worked against achieving interoperability, including but not limited to the high cost of designing and implementing custom interfaces to connect these systems, data standards gaps, lack of guidance to implement existing standards in registries, financial and other incentives and data blocking. A goal of the HL7 Common Clinical Registry Framework project is to lower barriers to achieving semantic interoperability for registries. The authors hope that the general registry DAM will provide guidance that supports those who develop and implement registries, EHRs and other CIS in enabling them to more easily interoperate and share information.

## Clinical Registries

Clinical registries are rapidly becoming important tools for advancing health care in a number of ways. Historically, registries have supported public health programs for conditions ranging from infectious diseases to cancer, by enabling the estimation of the prevalence or incidence and the data-driven understanding of disease etiology, and to support treatment and follow-up of cases over time. Clinical registries can support the design, planning, and recruitment by providing data to develop hypotheses and estimate the number of potentially eligible patients, as potential subjects to approach for enrollment in the study. Registries can also support scientific study by acting as a data source for observational comparative effectiveness research studies. Further, registries can be used to monitor the safety of new drugs, especially those whose long term outcomes are uncertain e.g., as they can provide large-scale, real-world safety and efficacy data on marketed drugs and combination therapies. The use of registries for post-market monitoring (Phase 4 studies) of approved drug products has increased in recent years, particularly for rare diseases. Under the FDA Amendments Act of 2007 in the United States, the FDA can mandate post-approval requirement studies and Risk Mitigation and Evaluation Systems as a condition of approval for new products with potential safety issues. As registries have become more common, demonstrations of registry-based (interventional) trials are moving forward. (4) (5)

All of these scientific and public health uses for registries feed into our understanding of disease and optimal methods for prevention and management. This “evidence” can then be applied to healthcare practice, and its impact can be measured, monitored, and improved. Registries can support this translation of evidence info improvement of care quality. Of increasing importance is the use of registry information to monitor care quality, supported by a number of national incentives to measure and improve performance. Registries, including Qualified Clinical Data Registries (QCDRs) - those qualified by CMS to measure and report clinical performance as part of participation in federal payment programs, focus on data collection directly related to patient encounters with the health care delivery system, across multiple provider organizations and care settings and including documentation of self-care and follow-up. A use of registry information that is also increasing in importance is the management of patient populations with chronic diseases, including examining broader health trends across factors including environmental, geographic and sociodemographic.

Despite the wide variety of registry functions, there is some commonality. All have the need to collect information about specific patients over varying periods of time, have a need for quality assurance, and to aggregate and report the data in support of various functions and purposes.

The specific requirements for data quality and assurance are determined by the primary purpose of the registry and any regulatory and sponsor requirements. Basic data requirements include: completeness of case ascertainment, extensive clinical data, verification of data validity, and follow-up. (6)

Of course, the verification of data validity and completeness of case ascertainment is a desirable feature for any registry, but for some purposes e.g., the use of registry information for scientific or epidemiologic investigation, the verification of data and assurance of complete case capture is of utmost importance, whereas in other applications, such as advertising for clinical trials, the lack of data verification or incomplete case ascertainment does not impede the registry objectives.

AHRQ’s *Registries for Evaluating Patient Outcomes: A User’s Guide* has become the definitive guide to gain an overall understanding of the considerations that apply to the different stages of the lifecycle of a registry, from initial conceptualization to eventual retirement. Readers are encouraged to review this guidance for elaborate description and case studies of the topics mentioned above. (1)

## Registry interoperability needs

## Drivers of interoperability include clinical and administrative uses cases that require or benefit from visibility to the complete picture of care across clinicians, care settings, provider organizations and over varying periods of time. As the health information infrastructure in the United States is fragmented, accomplishing many of those use cases on a national level requires linking data from multiple sources together in a way that preserves the meaning of the information and allows a single view into the data from which specific queries can be executed.

The aforementioned use cases, such as quality improvement, benchmarking, clinical research and performance evaluation for payment, increasingly need metrics that cut across multiple clinical areas. Our current national system of clinical registries provide high quality, specific rich clinical data in support of these purposes, but their data currently exist in silos and are typically not yet standardized from one registry to another. National efforts, even within a single clinical area, require the capture, transport and interpretation of data from multiple implementations of EHRs and other health IT. When measurement crosses clinical boundaries and data must be collected from multiple registries, the data must be linked in the same way that registries link data from multiple EHRs. This is currently a time-consuming and expensive process, and is typically not done outside of the most urgent circumstances.

Currently a significant proportion of EHR data are either unstructured free text, or if structured are not sufficiently standardized across health entities to allow the kind of national data collection and analysis without extensive effort to harmonize and normalize the data. The cost of this work, and the lack of incentives to support it for most use cases, means that it is typically not done. Greater adoption and use of common clinical data standards in registries and EHRs will lower barriers to automatically extracting information into registries, thus improving the feasibility of the kinds of national scale analyses they make possible.

Given increased demand for cross-cutting measures to drive value-based payment models, automated data capture as well as linking between registries is becoming more urgently needed to efficiently capture the needed data to drive performance measurement. If registries standardize their data elements, especially those that are common across clinical areas, as well as agree to implement technical standards that facilitate easier, data transfer, barriers to the effective use of registries to measure health care performance on a national level will be lowered.

## Registry standards needs

Currently, organizations, institutions and research groups create their own data elements, use their own data structures based on their own interpretation of the data and share data with registries using various modalities, including manual data entry, exporting data from an EHR and then transforming it to a registry format, or collecting data from other information systems and transforming it for submission to a registry. These process can be laborious and some registry steward organizations have governance structures specifically responsible for data transformation and registry submission. Given the increased demand for information from registries, manual entry and custom interfaces for automated extraction of data into registries from other health IT are not sustainable. Registries are responding to this opportunity by streamlining these processes. It is hoped that the HL7 registry DAM will facilitate the development of new infrastructure, including standards, to support these efforts.

## Data Standards

To share, aggregate, and exchange data efficiently, both semantic and functional interoperability is needed. With semantic interoperability both the sender and receiver of data have a common understanding or interpretation of the data and with functional interoperability, a set of common functions and procedures are implemented. To obtain semantic interoperability standard definitions, common words (data elements and terminology), organization and data structures (formats) are needed.Even in the case where a word in data being input into a registry appears to be the same, there may be a variety of definitions and/or differences in interpretation. This may result in data input into the registry in a way that does not necessarily preserve the meaning of the information. Thus, when analyzing these data or generating reports, the resulting information may not be accurate or valid. (7)

Creating data standards that can be used across all domains in healthcare, registries, research, quality improvement and other uses promotes improved data quality. According to the ISO 11179 standard, data standards should consist of a common or standard data element name, a definition and a set of permissible or allowable values. Data standards are developed by the clinical or domain stakeholders, vetted through a public process and published usually through a standards development organization (SDO).

SDOs such as HL7, ISO and the Clinical Data Standards Consortium (CDISC) are examples of organizations that create data standards for use in healthcare and research. HL7 follows the ANSI accredited process for standards development to ensure open contribution by the various community stakeholders. The HL7 Clinical Interoperability Council (CIC) is one group within HL7 that develops therapeutic area data standards with input from domain experts and clinicians. The CIC provides balloted standards to CDISC to be converted to their standards and to create CDISC Therapeutic Area User Guides for clinical trials. CDISC develops standards for regulatory and marketing approval, primarily FDA. ISO technical committee 215 develops health informatics standards. Developing data standards through an international SDO promotes a broader set of contributors and provides authority behind a standard because of the rigor and broad input. The HL7 DAM is a mechanism used to develop and ballot data standards.

## Functional Standards

Functional interoperability is necessary to reduce user burden, to facilitate data acquisition and data sharing across systems. Each registry usually has its own method for data acquisition, processing, input, navigation and function. Standardizing system functions will reduce the need for separate programming scripts, language and mechanisms for each specific data source and registry. HL7’s Structured Data Capture (SDC) is an example of a functional standard that provides a method for additional data collection for a specific need while a user is in the EHR screen. It is based on CDISC’s and Integrating the Healthcare Enterprise (IHE’s) Retrieve Form Data Capture (RFD). It is a standard that allows a form prepopulated with data from the EHR to be opened within the user interface and provides the ability for a user to enter data into that form. The form can be sent to a different database or data source such as a Registry. SDC further enhances the standard by using standard data elements to capture the data. The EHR Profile is another HL7 standard that indicates the functions of an EHR. This profile can be used to certify EHRs that meet interoperability specifications and it could be extended to include functions to facilitate interoperability across EHRs and registries. In addition, a functional profile for registries may provide basic functional criteria for all registry systems to lower the barriers to data exchange and sharing.

Many data elements and system functions are common across various domains, so it seems advantageous to use a common set for clinical use in the healthcare environment, research and across registries. Identifying, defining and implementing semantic and functional standards will reduce the barriers to data sharing, hopefully reduce manual resources and improve data quality.

## Exchange Standards

Currently, registries use a variety of methods to capture data directly and from source data systems. Provider organizations participating in registries must establish links between their CIS and each individual registry through custom interfaces. There is a need for a voluntary consensus among national clinical registries on a standardized way of exchanging data with other CIS and with each other.

## Common Models

Clinical registries capture data across a variety of clinical domains. The number of individual specific data elements needed to properly capture the information needed is vast. Many data elements are specific to particular clinical domains, however a significant proportion of the collected data, such as patient demographics, are common across domains. There is an opportunity for a multistakeholder convener of registries to establish voluntary common clinical data elements that may be implement across registries and their source data systems. In order for common clinical data elements to be efficiently implemented in health IT, they must be described using standard models. The HL7 Fast Healthcare Interoperability Resources (FHIR) standard may be used in developing the needed data standards and technical infrastructure to support the implementation of common models across registries and their source data systems.

## The HL7 DAM: key to identify data standards gaps and opportunities

DAMs are used by the HL7 to describe a domain. At a minimum they identify the data elements used in that domain, the activities, uses or use cases, describe the clinical setting through the use of story scenarios, and the relationship of the data elements to each other using a class model. To support registry interoperability, a DAM will be able to fully express the scope of the domain to evaluate which standards are available. A DAM can be a useful tool to identify commonality across registries, which will help to identify where existing standards may be useful and where there are gaps. It can also support efforts to develop the informatics solutions that are needed to successfully achieve semantic interoperability.

The clinical DAMs produced by HL7’s CIC are used to support or carry the clinical data elements, their definitions and the permissible or allowable values. The first clinical DAMs with standard data elements were balloted in 2008. There are many DAMs in HL7 that provide great descriptions of a clinical domain some may or may not have a list of data elements, with definitions and permissible or allowable values. See Table 1 for a list of HL7 DAMs.

**Table 1: HL7 DAMs**

| DAM | HL7 Work Group steward |
| --- | --- |
| Allergy and Intolerance | Patient Care |
| Behavioral Health Record | Community Based Collaborative Care |
| Bipolar Disorder | Clinical Interoperability Council |
| Cardiology DAM (Acute Coronary Syndrome) | Clinical Interoperability Council |
| Cardiology (Common Data Elements) | Clinical Interoperability Council |
| Care Plan | Patient Care |
| Clinical Trials Registration and Results | Regulated Clinical Research Interoperability Model |
| Detailed Clinical Models | Patient Care |
| Data Elements for Emergency Department Systems | Emergency Care |
| Diet and Nutrition Orders | Patient Care |
| Emergency Medical Services | Clinical Interoperability Council |
| General Anxiety Disorder\* | Clinical Interoperability Council |
| Health Quality Improvement | Clinical Quality Information |
| Immunization | PHER |
| Laboratory Orders | Pharmacy |
| Major Depressive Disorder | Clinical Interoperability Council |
| Pressure Ulcer Prevention | Patient Care |
| Preoperative Anesthesiology (co-sponsored w/ Anesthesia WG) | Anesthesia |
| Schizophrenia | Clinical Interoperability Council |
| Specimen | Genomics |
| Trauma Registry Data Submission | Clinical Interoperability Council |
| Tuberculosis (Pulmonary Adult) | Clinical Interoperability Council |
| Tuberculosis (Pediatric) | Clinical Interoperability Council |
| Vital Records | Public Health and Emergency Response |

\*Pending Ballot

Within HL7, the development of a DAM is often a precursor to development of one or more message exchange, document structure, or resource specification standards. The DAM provides a consistent method of documenting interoperability requirements by specifying the actors involved, the use cases and activities that give rise to the need for data exchange, and the data elements that comprise the content of information exchange packages. A DAM is implementation technology agnostic. It can be used as a common set of requirements for HL7 v2 or v3 messages, CDA structured document implementation guides, FHIR resource and resource profile specifications, and payload definitions in Service Oriented Architecture (SOA) functional specifications.

### A DAM for registries – Common Clinical Registry Framework

The Common Clinical Registry Framework (CCRF) DAM was developed under auspices of the HL7 Clinical Interoperability Council (CIC) workgroup with participation from national and international registry operators, industry groups, vendors, and clinical registry participants. The content of the CCRF DAM draws heavily upon the guidance provided in the AHRQ Handbook for Registries ([Registries for Evaluating Patient Outcomes: A User's Guide: 3rd Edition](http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?pageaction=displayproduct&productid=1897)), the collective wisdom and experience of the CCRF project team, and contributions by third party reviewers.

Work on the CCRF began with identification of nine high-level uses cases common to clinical registries. The use case model formed the foundation for all subsequent modeling activities. An activity model was constructed detailing the sequence of activities for each use case and the flow of information between actors defined in the use case model.

The information flows between activities were defined and further detailed in the form of class diagrams. The individual information flow class diagrams were subsequently combined into a single comprehensive CCRF Data Model.

The portion of the CCRF Data Model that covered the content and structure of a general clinical registry was further detailed to include class attributes and attribute terminology bindings for datatypes considered to the be core elements shared in common among clinical registries. The HL7 [Reference Information Model (RIM)](http://www.hl7.org/implement/standards/product_brief.cfm?product_id=77) was used as a framework for expressing these common elements as abstract concepts which can be easily transformed into HL7 interoperability constructs such as message, document, and resource specifications.

**Figure 1 - CCRF DAM Use Case Diagram**

The latest version of the CCRF DAM can be found on the HL7 wiki at <location>

The CCRF DAM will be published as an HL7 informative specification. As portions of the DAM are used to derive downstream interoperability standards, those portions will be included as part of the normative materials for those specifications. If and when significant portions of the DAM have been included in subsequent normative materials, the DAM itself will be balloted and published as a normative specification.

## Conclusion

This DAM was developed to address the need for an underlying conceptual model for registries that can support the growing number of registries and associated requirements for interoperability with EHRs and other health IT. The use of registries has grown tremendously over the past decade to support a number of quality improvement, research, chronic disease management and other purposes. The use of information from disease- or procedure-specific clinical registries will continue to grow as medical specialty and health care professional societies and associations, organizations representing patients and consumers, payers and others ask for it. As the technology becomes familiar, more registry vendors and consultants are advertising the benefits of registries to potential sponsors, further increasing the need. In particular, national incentives for value-based care have created an immediate business need for organizations to manage specific chronic disease, improve population based outcomes and comply with national requirements for reporting of quality metrics.

The demand for registries has created a promising business area for software and technology developers, particularly those engaged in other types of regulated human research and the development of clinical EHR systems. Just as the large number of different EHR development companies has brought a variety of EHR designs and data and information models and a proliferation of data standards, the large number of registry developers and service providers threatens to add variety and complexity of the task of integrating clinical and health data into registries. Standardization of clinical data both in registries and in source data systems, along with exchange specifications that support interoperability can bring new efficiencies to the exchange of data between healthcare providers, registries, and patients.

The CCRF DAM provides a conceptual framework that can serve as a common foundation for a number of software applications that support registry operations or data exchange. As with any model, our DAM needs vetting and validation from potential users. We invite registry providers, sponsors, and developers to review our model and identify missing activities or relationships that can be included. The HL7 balloting process will further support review of our DAM across a broad spectrum of stakeholders and perspectives, leading to improvement and validation of the model. In addition, the HL7 modeling process will ensure that the CCRF DAM will complement other domain specific DAMs as well as different EHR functional models that underlie EHR applications and other health IT systems.

EHR developers and health care organizations that must transmit EHR data to different registries should inform the refinement and validation of this model. The healthcare organizations and registry sponsors might ultimately be the users most likely to benefit from this model and the efficiencies in information exchange that it will enable. We are hopeful that such organizations will soon demonstrate data exchange between EHRs and registries, and move beyond proof of concept to demonstration of utility, as measured by improvements in business efficiency or patient outcomes.

To this end, we will continue to engage groups in the evolution of the CCRF DAM. A diverse group of contributors will help identify multiple and new ways to demonstrate the value of standards and our CCRF DAM.

In the future, our efforts should address emerging policies and regulations around interoperability or data reporting and data standards. For example, research sponsors that are supporting a registry can require the use of common data elements, and DHHS or NIH could support data element registries or data dictionaries. Other standards related to patient reported data and genetic data are evolving rapidly but should be endorsed as soon as possible to ensure that registries co-evolve with EHR and clinical data standards.

# Bibliography

1. **Gliklich, R. & Dreyer, N.** *Registries for Evaluating Patient Outcomes: A User's Guide. Third Edition.* Rockville, MD : Agency for Healthcare Research and Quality, 2014.

2. **HIMSS.** *HIMSS Dictionary of Healthcare Information Technology Terms, Acronyms and Organizations. 3rd Edition.* s.l. : HIMSS, 2013.

3. **ONC.** Standards Advisory. *healthit.gov.* [Online] 2016. https://www.healthit.gov/standards-advisory.

4. **FDA.** *Guidance for Industry and FDA Staff. Procedures for handling post-approval studies imposed by PMA order.* Rockville, MD : FDA, 2007.

5. *Registry-based randomized clinical trials - a new clinical trial paradigm.* **James, Stefan et al.** 5, s.l. : Nature Reviews Cardiology, 2015, Vol. 12.

6. *Patient registries: utility, validity and inference.* **Richesson R., Vehik K.** s.l. : Advances in Experimental Medicine and Biology, 2010.

7. *The making and adoption of health data standards.* **Hammond, W. Ed.** s.l. : Health Affairs, 20015, Vol. 24.5, pp. 1205-1210.