Best Practices for Implementation and Development of Data Models and Data Structures based on FHIR: A Systematic Review

Parinaz Tabari[1*], Gennaro Costagliola[2], Mattia De Rosa[3], Martin Boeker[3]

[1]Department of Informatics, University of Salerno, Via Giovanni Paolo II, Fisciano, 84084, SA, Italy.
[2]Institute of Artificial Intelligence and Informatics in Medicine (AIIM), Chair of Medical Informatics, University Hospital rechts der Isar, School of Medicine, Technical University of Munich, Ismaninger Straße 22 , Munich, 81675, Bavaria, Germany.

*Corresponding author(s). E-mail(s): ptabari@unisa.it;
Contributing authors: gencos@unisa.it; matderosa@unisa.it; martin.boeker@tum.de;

Abstract

Purpose: This study seeks to investigate data models that utilized the Fast Healthcare Interoperability Resources (FHIR) standard in an attempt to offer a comprehensive overview of the best practices for developing and implementing these data models.
Methods: To conduct this study, we utilized the instructions for Systematic Literature Review (SLR) for computer science. We analyzed the indexed articles in PubMed, Scopus, Web of Science, IEEE Xplore, ACM digital library, and Google Scholar using Boolean operators "AND" and "OR" to merge the above-mentioned keywords and retrieve the desired articles.
Results: Based on the reviewed articles, we categorized the articles into two main groups; pipeline-based data models and non-linear data models. **Conclusion:**

Keywords: FHIR, Fast Healthcare Interoperability Resources, data model, modeling

1 Introduction

In the field of informatics, operations and data structures can be described by a set of concepts called data models. Since structures and data points are needed to be connected in order to represent connections, data modeling offers a visual representation of the system, either in whole or in part. As an instance, one of the most commonly-used conceptual data models is the Entity Relationship (ER) model which is generally linked with a relational database [1]. Data modeling is a process that defines how the data should be maintained in a database. Data types, constraints, relationships, and metadata definitions are among the features that are specified by a data model [2]. Data models can also play a crucial role in boosting the possibility of clinical research and taking full advantage of clinical data stored in medical systems; data, as well as the clear relationships between them, are expected to be in a standardized format in order to establish reproducible research [3].

Furthermore, data modeling can facilitate interoperability between medical systems. Interoperability refers to the ability to exchange and utilize information between computer systems, which is essential in various fields such as artificial intelligence (AI), big data research and analytics, medical communication, and multinational collaboration. In the medical field, interoperable systems can reduce errors and documentation workload, empower patients, and facilitate information retrieval. In research, real-world information can be collected and used for data mining and AI to generate new hypotheses [4]. The management board of the Healthcare Information and Management Systems Society (HIMSS) defined three levels of interoperability: Fundamental, Structural, and Semantic. Fundamental interoperability refers to the communication method between IT firms and devices, structural interoperability is the format of data being communicated and semantic interoperability is when systems can communicate and use information autonomously [5].

Obviously, developing a data model would contribute to enhancing structural interoperability between medical information systems. The efficient data exchange will contribute to the reduction of time and financial resources [6]. HL7 is a collection of standards aimed at improving information exchange between health-related systems, making it a fundamental standard for implementing Electronic Health Records (EHRs). HL7 V2 and V3 were released before the development of Fast Healthcare Interoperability Resources (FHIR), the most recent interoperability standard by HL7 [7]. FHIR mapping is regarded as determining the syntactic and semantic corresponding FHIR resources to real-world data elements, which can be a distinguished step in the FHIR data modeling procedure [8].

1.1 FHIR-Related Definitions

In this section, the most important definitions related to FHIR will be clarified in order to enhance comprehension when reading the paper.

- **Resource:** The concept of FHIR "Resources" is a collection of modular parts that make up the foundation of HL7 FHIR. These resources constitute the fundamental data exchange model and format of FHIR. An exchangeable patient record's core data elements, limitations, and associations are determined by the resources [9].
- **Profile and Extension:** A profile is a formal definition of how a specific resource or set of resources should be used in a particular context. An extension is a way to add additional data elements to a resource that are not part of the base definition of the resource. Profiles may contain extensions as well as required and optional data elements [10].
- **Bundle:** Gathering a number of resources into a single instance with an enclosing context is a frequent task done with FHIR resources. This is known as "bundling" the resources together [11].
- **Code System and Value Set:** Code systems specify which codes exist, and how they are defined and understood. To describe which codes can be used in a given situation, value sets choose a set of codes from one or more code systems [12].
- **Implementation Guide (IG)**: IG is a collection of rules about the usage of FHIR resources considering a specific problem of interest. After being generated by the FHIR IG publisher, IGs are published online [13]. IG is a document for the implementation of profiles.

1.2 Why FHIR data models?

It is believed that using the FHIR standard for clinical data representation would be a practical methodology to enhance and accelerate data availability for research. These models can also have the potential to be transformed into other models for analytics purposes [14]. In addition, FHIR-based data normalization pipelines are considered valuable tools in data capturing and EHR phenotyping [15]. For instance, there is a pipeline called NLP2FHIR that can be utilized to standardize unstructured EHR data [16]. In general, it is possible to formalize and integrate unstructured and structured EHR data by a FHIR-based framework [17]. With respect to the big data domain, workflows of data harmonization pipelines integrated with FHIR would present a scalable data modeling of large datasets [18]. It is also feasible to use FHIR data models to standardize heterogeneous annotation corpora [19]. All the mentioned potentials will obviously lead to better interoperability between medical systems, either directly or indirectly.

1.3 Research Objectives (Objs)

In this research, we aimed to provide a comprehensive overview of the best practices of data modeling based on the FHIR standard and determine the methodologies, opportunities, and limitations in developing these models.

- Obj1: To provide an overview of data models based on FHIR in the context of interoperability, structure, and functionality and summarize the best practices for developing FHIR-based data models
- Obj2: To highlight limitations, challenges, advantages, and opportunities brought about by FHIR data models
- Obj3: Proposing a general architecture for developing FHIR-based data models

1.4 Paper structure

Section 2 provides the detailed methods of conducting the review, including research design, scientific resources, search strategy, inclusion/exclusion criteria, research questions, scanning and relevance, and data extraction. Section 3 deals with the description of the obtained results, section 4 discusses the results, and section 5 concludes the research.

2 Planning and Methods

To conduct this study, we utilized the instructions for Systematic Literature Review (SLR) for computer science research presented by Carrera-Rivera et al. SLR is a research methodology to gather information on a specific topic and analyze it in a critical and systematic manner [20]. In the following subsections, we highlight the detailed methodology of the planning procedure.

2.1 Planning Step I: Defining PICOC

To define *Population, Intervention, Comparison, Outcome, and Context (PICOC)* [21], we break down research objectives into the following definitions presented in Table 1.

Table 1: Defining PICOC

	Definition
Population	Healthcare systems, patients, practitioners
Intervention	Using FHIR data models
Comparison	Different types of data models
Outcome	Improved interoperability, efficiency, patient outcomes
Context	Technical health infrastructure, Clinical domain

2.2 Planning Step II: Research Questions (RQs)

To accomplish the research objectives, the following questions will be answered:

- RQ1: What are the state-of-the-art and best practices in developing FHIR data models?
- RQ2: Which aspects of medicine or fields of application are more involved in FHIR data modeling?
- RQ3: How does the FHIR standard increase interoperability when applied to clinical data models?
- RQ4: Which tools, standards, terminologies, and models were used most in developing data models?
- RQ5: Which FHIR resources were used most in developing data models?
- RQ6: What are the barriers, challenges, and opportunities of developing FHIR-based data models in the healthcare domain?
- RQ7: What would be a general procedure for developing or proposing a FHIR-based data model?

  It should be noted that the research questions will accomplish the objectives. For instance, RQ6 is associated with Obj2, and RQ7 is associated with Obj3. All other questions are associated with Obj1.

2.3 Planning Step III: Keywords and Digital Libraries

To extract relevant information about the topic, the most important academic libraries were thoroughly investigated. The keywords we selected to define search strategies include, FHIR, data model, data element, modeling, and minimum dataset.

Justifications of selecting the keywords of search:

- FHIR: The standard of focus in this research
- Data model: This keyword captures articles that discuss data modeling in general, which can include FHIR data models in healthcare
- Data element: This keyword focuses on individual components or fields within a data model. Including this keyword helps us to identify articles that specifically address the definition and representation of data elements within FHIR data models
- Modeling/Modelling: This keyword broadens the scope of our search to include articles that discuss modeling techniques and methodologies in the context of healthcare data, including FHIR data models
- Minimum dataset: This keyword is relevant because we are interested in articles that discuss the concept of minimum datasets within the FHIR data modeling approach. It can help us identify articles that focus on defining the essential set of data elements needed for specific purposes

We analyzed the articles indexed in PubMed, Scopus, Web of Science, IEEE Xplore, ACM digital library, and Google Scholar using Boolean operators "AND" and "OR" to merge the above-mentioned keywords and retrieve desired articles. It is worth mentioning that no time limit was applied to the search in an attempt to obtain a comprehensive overview of all published articles in this field. We should clarify that only the initial pages of Google Scholar (9-10 pages) were investigated as a supplement to academic libraries.

2.3.1 Building Search Strings

After defining the research plan, the study was officially conducted based on the steps discussed previously. We initially investigated scientific databases based on written search strategies. Table 2 illustrates the academic databases and the search strategies for each one as well as the number of retrieved articles. The search was conducted in May 2023.

Table 2: Strategies to Search in Academic Databases

Database	Search strategy	Retrieved articles (N.)
Scopus	(TITLE-ABS-KEY(”fhir” OR ”fast healthcare interoperability resources”)) AND (TITLE-ABS-KEY(”data model” OR ”modelling” OR ”modeling” OR ”MDS” OR ”minimum data set” OR ”minimum dataset” OR ”data element*”))	175
PubMed	(((((((data model[Title/Abstract]) OR (modelling[Title/Abstract])) OR (modeling[Title/Abstract])) OR (MDS[Title/Abstract])) OR (minimum data set[Title/Abstract])) OR (minimum dataset[Title/Abstract])) OR (data element*[Title/Abstract])) AND ((fhir[Title/Abstract]) OR (fast healthcare interoperability resources[Title/Abstract]))	114
WoS	AB=(”fhir” OR ”fast healthcare interoperability resources”) AND AB=(”data model” OR ”modelling” OR ”modeling” OR ”MDS” OR ”minimum data set” OR ”minimum dataset” OR ”data element*”)	59
IEEE Xplore	((”fhir” OR ”fast healthcare interoperability resources”) AND (”data model” OR ”modelling” OR ”modeling” OR ”MDS” OR ”minimum data set” OR ”minimum dataset” OR ”data element*”))	17
ACM	[[Abstract: ”fhir”] OR [Abstract: ”fast healthcare interoperability resources”]] AND [[Abstract: ”data model”] OR [Abstract: ”modelling”] OR [Abstract: ”modeling”] OR [Abstract: ”mds”] OR [Abstract: ”minimum data set”] OR [Abstract: ”minimum dataset”] OR [Abstract: ”data element*”]]	10
Google Scholar	*((”fhir” OR ”fast healthcare interoperability resources”) AND (”data model” OR ”modelling” OR ”modeling” OR ”MDS” OR ”minimum data set” OR ”minimum dataset” OR ”data element*”))*	*91*

2.4 Planning Step IV: Inclusion/Exclusion Criteria

In order to select initial studies and define relevant articles for the next phase, we developed some inclusion and exclusion criteria. By using the following criteria, we could select the articles of interest based on title/abstract and rapid skimming method of some full-texts. We employed EndNote software for article screening and investigation in each step.

A) Inclusion Criteria (IC):

- IC1: Original articles and case studies published in journals and conferences
- IC2: High-quality articles relevant to research questions that can present best practices for developing FHIR-based data models; in particular, articles with FHIR-based data models specifically designed or applied to a disease or a group of related diseases (practical approach/real-world data),
- IC3: Articles with high-quality and detailed workflow processes with at least one architecture/data model diagram

B) Exclusion Criteria (EC):

- EC1: Not written in the English language
- EC2: No full-text available or not accessible
- EC3: Letter to the editors, editorials, commentary articles, short papers without detailed implementation information, posters, and pre-print articles
- EC4: Review articles
- EC5: Not relevant to research questions and objectives; in other words, articles that do not provide practical and detailed insights into the development or use of FHIR-based data models
- EC6: Low-quality articles

2.5 Planning Step V: Scanning and Relevance

After the initial investigation of the articles and selecting them based on reading the title/abstract and skimming some articles, we further assessed and scanned the full texts of initially selected articles based on relevance to our research questions and objectives.

2.6 Planning Step VI: Data Extraction Form

After defining the final articles, data will be extracted from them based on the following data fields presented in the articles:

- Bibliographic information, such as title, authors, and year of publication
- FHIR resources used in the development
- Data sources
- Data transformation and mapping
- Standards/tools/terminologies/models
- Data validation/evaluation
- Use cases/applications
- limitations/challenges
- Summary of the findings, outcome, or contribution

  ** It should be mentioned that the last two items (i.e., limitations and contributions) will be discussed in separate sections (section 3.3 - section 1.2 and section 4) and not included in the main tables.

3 Review Report

Of the overall 466 articles found during the comprehensive search based on the strategies in Table 2, 238 studies were duplicates. Of the remaining 228 articles, 120 articles were excluded based on reading titles/abstracts or skimming some full texts, which left us with 108 articles for the next phase. In the eligibility phase, the remaining articles were investigated by **thoroughly reading and scanning** full texts and then assigned to one of the two groups. Of these articles, **27** articles were eventually selected to be included in this review. Fig 1 illustrates the *Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA)* chart [22] of this study.

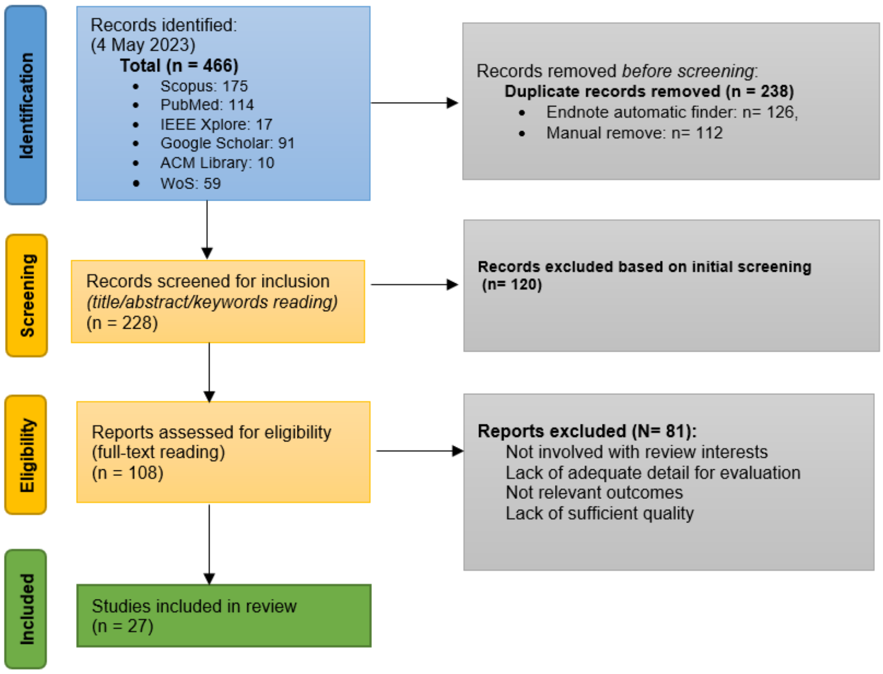

Fig. 1: PRISMA chart for the systematic review

3.1 Model Types

From analyzing the full texts of the articles, we understood that there could be two main types of developing and presenting data models based on the FHIR standard;

- **Pipeline-based data models**
- **Non-linear data models**

3.1.1 Pipeline-Based Data Models

In this section, the articles related to the use of the FHIR standard in data pipelines will be discussed. Out of 27 included articles, **21** of them were related to the development of pipeline-based data models using the FHIR standard. Data pipelines are chains of functions and activities that lead the input to the output in an attempt for the flow of data to be smooth and automated from source to destination [23]. Pipeline-based data models deal with the process of moving, transforming, and analyzing the data using FHIR standards. In other words, this type of model is a specific implementation of FHIR data models in the context of data integration, transformation, or processing. The FHIR standard can be utilized as a canonical data model to develop pipeline models. Table 3 summarizes the extracted information about this category.

Table 3: Pipeline-based data models

Authors	FHIR resources/elements used	Data source	Data transformation and mapping	Standards, tools, terminologies, models	Validation, evaluation	Use cases, applications
Lenert et al [14]	Patient, Encounter, Condition, Procedure, MedicationRequest, MedicationAdministration, Observation	Epic EHR, large academic institution	flat file to FHIR, FHIR to OMOP, FHIR to PCORnet	HL7 v2.X, OMOP, PCORnet, Flat file, FHIR CDR, CDM	by published quality assessment tools	healthcare research, especially in the context of covid-19
Wen et al [24]	Composition, ValueSet	i2b2 Obesity Challenge dataset, MIMIC III obesity discharge summaries	FHIR-based NLP extensions to CQL, FHIR extensions to NLP2FHIR pipeline	NLP2FHIR pipeline, CQL, NLP engines (cTAKES, MEDXN, MedTime), PheKB	Phenotype algorithms in PheKB, obesity phenotyping algorithm plus two obesity datasets	Obesity
Hong et al [15]	composition, condition, MedicationStatement, Procedure, FamilyMemberHistory	i2b2 obesity challenge (discharge summaries)	EHR data to FHIR resources	NLP tools (cTAKES, MedXN, MedTime), NLP2FHIR pipeline, machine learning algorithms (logistic regression, support vector machine, decision tree, and random forest)	Using MIMIC-III obesity dataset as a second dataset, evaluation measures (P, R, F1) for performance evaluation	Obesity
Hong et al [16]	Composition, Condition, Observation, Procedure, MedicationStatement, Medication, FamilyMemberHistory	Mayo clinic's unstructured EHR data	unstructured and structured EHR data to FHIR resources	NLP2FHIR pipeline, UIMA clinical NLP tools (cTAKES, MedXN, MedTime), LOINC, SNOMED CT, RxNorm, ATC	reusing annotation corpora, standardizing annotation corpora, NLP2FHIR performance evaluation by P, R, F1	randomly collected notes
Zong et al [25]	Questionnaire, QuestionnaireResponse	Mayo Clinic patients with colorectal cancer, ACP	unstructured reports to structured reports, synoptic report to ACP, ACP FHIR model to CRF	NLP tools, UDP data sources	P, R, F1, Accuracy	colorectal cancer
Hong et al [17]	MedicationStatement	Medication data from Mayo Clinic's EHR	unstructured EHR data to FHIR, structured data to FHIR resource, FHIR resources to annotation schemas	NLP tools (MedXN, MedTime), rule-based approach, CAS, RxNorm, UIMA, protégé	P, R, F1	randomly selected notes
Williams et al [18]	Patient, Encounter, Observation, Procedure, MedicationRequest, MedicationAdministration, Condition	MIMIC IV database for validation	raw hospital records to AI-friendly and harmonized representation, database tables to FHIR standard	ETL framework, Postgres	openly available MIMIC IV database to test FHIR-DHP, syntactic validation of FHIR mapping	intensive care

Continued on next page

Table 3 – continued from previous page

Authors	FHIR resources/elements used	Data source	Data transformation and mapping	Standards, tools, terminologies, models	Validation, evaluation	Use cases, applications
Fischer et al [26]	Patient, Encounter, Observation	German PH registry	CSV file to FHIR bundle collection, source filed names to standard terminology (SNOMED-CT, LOINC, ATC, ICD-10), source data to OMOP schema	ETL process, XSLT, OMOP CDM, SNOMED-CT, LOINC, ATC, ICD-10	feasibility assessment by computation time and source data coverage in the target CDM	PH registry
Pfaff et al [27]	Patient, Encounter, Condition, Procedure, Observation, MedicationRequest, Practitioner	i2b2	CDM to FHIR	CDM, FHIR PIT	comparison of generated data by the pipeline and equivalent clinical data of CDWH warehouse	Asthma
Rosenau et al [28]	Condition, Observation, Procedure, MedicationStatement, Immunization, DiagnosticReport, Specimen	GECCO	clinical data to FHIR, SQ to FHIR search and CQL requests	SNOMED CT, LOINC, ICD-10-GM, ATC, CQL, ETL processes	create test patients, automated and manual test	covid-19
Zong et al [29]	Observation, Condition, Medication, FamilyMemberHistory, Patient	Mayo Clinic clinical data warehouse	clinical entries to FHIR resources, FHIR to RDF	RDF, classification, Machine learning and deep learning, cTAKES, MedXN, MedTime, NLP2FHIR, bag of features, Node2vec, ICD-9, RxNorm, LOINC	conventional 10-fold cross-validation, AUROC, AUPRC	Cancer
Bennett et al [30]	**FHIR base resources, resources in MIMIC: CodeSystem, ValueSet, FHIR categories: administration, organizational, orders, specimen observation, charted observation, medication, MedicationRequest, MedicationDispense, MedicationAdministration	MIMIC-IV	MIMIC-IV to FHIR	FSH, py mimic FHIR package, PostgreSQL, SNOMED CT	validation by open source FHIR server (HAPI FHIR) by bundles	intensive care (ED data)
El-Sappagh et al [31]	Patient, Practitioner, RelatedPerson, Observation, Condition, BodySite, AdverseEvent, AllergyIntolerance, Location, FamilyMemberHistory, CarePlan, Goal, NutritionOrder, Medication, MedicationRequest, *Dosage, MedicationStatement, Device, Encounter, EpisodeOfCare, CareTeam, Procedure, Element	WBAN, patient profiles in EHR, manual data sent by patients	RDB to FHIR, FHIR to RDB, EHR data to FHIR, direct mapping of historical data to FASTO ontology	FASTO ontology, OWL 2, WBAN, CDSS, Protégé, PHR, ISO IEEE 11073, LOINC, SNOMED CT, UoM, FHRBase database, FHIR RESTful, OAuth2, SPARQL, D2RQ platform, Jena API, Pallet and HermiT reasoners, CPG	Ontology is evaluated (assessment of correctness, consistency and completeness of ontology knowledge), Manual evaluation by experts	type 1 diabetes mellitus (T1D)
Zong et al [32]	DiagnosticReport, Observation	ACP, clinical records of Mayo Clinic's patients	structured and unstructured data to FHIR-based data profile, directly-inherited data element mapping	CRF, DMM model, ETL process, topic modeling	P, R, F1	Cancer clinical trials-colorectal
Hong et al [33]	Patient, Observation, Condition, Procedure	Ovarian cancer database, Lab-test database, CDM database	local code to standard code, lab test codes to LOINC codes, mapping between local identifiers and FHIR resource identifiers	Shiny web framework, Shiny apps library, R packages for FHIR data visualization, HAPI FHIR API, LOINC, ICD, CPT	feasibility and adaptability test using public FHIR servers	Ovarian Cancer

Continued on next page

Table 3 – continued from previous page

Authors	FHIR resources/elements used	Data source	Data transformation and mapping	Standards, tools, terminologies, models	Validation, evaluation	Use cases, applications
Hong et al [19]	Condition, FamilyMemberHistory, Procedure, Observation, MedicationStatement, Medication	three annotated corpora from SHARPn project, MedXN project, active Mayo's clinical NLP project (Family History NLP Project)	Source annotation schemas and FHIR annotation schema	UMLS, SNOMED CT, LOINC, RxNorm, NLP tasks, SVM, annotation tools (Knowtator, Anafora), Protégé ontology editor, HAPI FHIR API	evaluation with annotation corpora, calculated P, R, F1	annotated clinical notes
Marteau et al [34]	not defined	SHC data repositories, Synthea Patient Generator	map OMOP CDM concepts to FHIR resources by OMOP-on-FHIR (a novel clinical infrastructure)	ETL processes, OMOP CDM, PostgreSQL, psql, SMART on FHIR, Synthea Patient Generator	qualitative feedback collection, SUS	pediatric musculoskeletal disorders
Ismail et al [35]	Patient, Observation, Condition, Practitioner	MCHHJ and CRMHIS	data elements to FHIR resources	MongoDB, FHIR RESTful web services, DAO, Google's REST console application	user study and questionnaires, generate requests and view responses	Maternal health
Guinez-Molinos et al [36]	Patient, Specimen, DiagnosticReport, Observation	UC Christus laboratory	minimum dataset fields to FHIR	HAPI FHIR libraries, BPMN, Cawemo, clinFHIR graphBuilder, JSON Web Token (JWT), MySQL	performance evaluation (response time, throughput, process management time, main memory storage, secondary storage), usability test	PCR SARS-CoV-2 tests
Burkhardt et al [37]	Patient, Organization, Communication Consent, Quationnaire, QuestionnaireResponse, CarePlan	requirement analysis outputs (undergraduate students were surveyed)	data elements to FHIR	FHIR RESTful API, FHIR Search API, Google's Flutter, Keycloak, HAPI FHIR, AWS, Docker, Postgres DB, JWT, Apache web server	not stated	COVID-19 symptom tracking
De et al [38]	Patient, Practitioner, RelatedPerson, Organization, HealthcareService, Appointment, Device, Encounter, DocumentReference, AllergyIntolerance, AdverseEvent, BodyStructure, Specimen, Procedure, FamilyMemberHistory, Observation, Condition, Medication, Immunization, CarePlan, ExplanationOfBenefit, Account	the online patient portal at the Mayo Clinic Rochester	Biomedical text to UMLS, patient secure messages to hidden micro-concepts	MetaMap, LDA, Multi-purpose Annotation Environment, FHIR definitions	F1 score to check the consistency between annotators	Randomly sampled secure patient messages

Abbreviations: EHR: Electronic Health Record, **OMOP:** Observational Medical Outcomes Partnership, **PCORnet:** Patient-Centered Outcomes Research Network, **HL7:** Health Level 7, **CDR:** Clinical Data Repositories, **CDM:** Common Data Model, **i2b2:** integrating informatics for integrating biology and bedside, **MIMIC:** Medical Information Mart for Intensive Care, **NLP:** Natural Language Processing, **CQL:** Clinical Quality language, **PheKB:** Phenotype KnowledgeBase, **P:** Precision, **R:** Recall, **F1:** F-measure, **UIMA:** Unstructured Information Management Architecture, **LOINC:** Logical Observation Identifiers Names and Codes, **SNOMED CT:** Systemized Nomenclature of Medicine – Clinical Terms, **RxNorm:** medical prescription normalized, **ACP** Australian Colorectal Cancer Profile, **CRF:** Case Report Form, **UDP:** Unified Data Platform, **CAS:** Common Analysis System, **ETL:** Extract Transform Load, **AI:** Artificial Intelligence, **PIT:** Patient data Integration Tool, **CDWH:** Carolina Data Warehouse for Health, **GECCO:** German Corona Consensus Dataset, **ICD-10-GM:** International Classification of Disease-German Modification, **ATC:** Anatomical Therapeutic Chemical, **PH:** Pulmonery Hypertension, **XSLT:** Extensible Stylesheet Language Transformations, **RDF:** Resource Description Framework, **AUROC:** Area Under the Receiver Operating Characteristic Curve, **AUPRC:** Area Under the Precision-Recall Curve, **FSH:** FHIR SHorthand, **ED:** Emergency Department, **WBAN:** Wireless Body Area Network, **RDB:** Relational Database, **FASTO:** FHIR and SSN-based T1D, **OWL**: Web Ontology Language, **CDSS:** Clinical Decision Support System, **PHR:** Personal Health Record, **UoM:** Units of Measurement, **REST:** Representational state transfer, **OAuth:** Open Authorization, **CPG:** Clinical Practice Guideline, **psql:** A terminal-based front-end to PostgreSQL, **DMM:** Dirichlet Multinomial Mixture, **CPT:** Current Procedural Terminology, **SVM:** Support Vector Machine, **SHC:** Shriner's Children, **SUS:** System Usability Scale, **MCHHJ**: Maternal and Child Health Handbook in Japan, **CRMHIS:** Common Requirements for Maternal Health Information Systems, **DAO:** Data Access Objects, **BPMN:** Business Process Model and Notation, **JWT:** JavaScript Object Notation, **PCR:** polymerase chain reaction, **AWS:** Amazon Web Service, **LDA:** latent Dirichlet allocation

Since we aimed to know which aspects of medicine performed data modeling using FHIR (RQ2), we categorized the articles based on the medical use cases and healthcare domains.

A) Chronic Conditions/Diseases:

In the field of Natural Language Processing (NLP), there is a FHIR-related clinical data normalization pipeline called NLP2FHIR for EHR data modeling. This pipeline can be utilized in order to standardize and integrate structured and unstructured data stored in EHRs. FHIR extensions can be integrated into this pipeline to support next-generation EHR-driven phenotyping. A standard-driven approach called CQL4NLP was developed by Wen et al in an attempt to integrate a collection of NLP extensions represented in the HL7 FHIR standard into the clinical quality language (CQL) for EHR-driven phenotyping, in this case, obesity comorbidities [24]. In another research in the context of chronic conditions, NLP2FHIR was used to automatically analyze and understand the information in medical records. Hong et al made some improvements to this pipeline specifically for their study on obesity. These improvements included better ways of detecting different sections of the medical records and identifying important concepts and states of obesity [15]. Fischer et al integrated heterogeneous data of pulmonary hypertension registry to OMOP-CDM data standard. Common parameters were initially identified followed by mapping to LOINC and SNOMED-CT as standard terminologies. Extracted data in the form of FHIR bundles were then transformed to OMOP-CDM by XSLT [26]. The aim of another research in this area was to map source variables to FHIR data elements as well as map their value sets. The researchers developed a tool named Clinical Asset Mapping Program for FHIR (CAMP FHIR) to read CDMs (such as i2b2 and PCORnet data models) and map the items to FHIR [27]. Marteau et al utilized a technology named OMOP-on-FHIR to convert data elements in OMOP-CDM format to FHIR standard. The researchers also used FHIR data elements to implement two apps to facilitate cohort administration in the context of pediatric musculoskeletal diseases research [34]. El-Sappagh et al integrated the FHIR standard and the SSN sensor ontology to implement a cloud-based mobile health system for monitoring and treatment of type 1 diabetes mellitus patients. The system also presented semantic CDSS capabilities based on FASTO ontology [31].

B) Covid-19:

In the context of COVID-19, an approach presented by Lenert et al. was used to federate clinical data across sites by maintaining a single master patient identifier and consistent demographic information. Additionally, the proposed pipeline was asserted to be used to distribute data across networks and maintain shared data elements such as mortality status and social determinants of health data. In the mentioned approach, the data were loaded in FHIR CDR which eventually produced real-time linked repositories including FHIR, OMOP, and PCORnet. The researchers found that using FHIR as an initial canonical data model and FHIR subscription protocols for transformation and synchronization of multiple data models has potential benefits for healthcare research, including the automated production of research data marts for COVID-19 research [14]. Guinez-Molinos et al developed an interoperable platform for reporting PCR SARS-CoV-2 tests. The researchers created a MDS for the tests followed by modeling related processes and endpoints. The implementation continued with designing standards and interoperability and software development, testing, and implementation [36]. Burkhardt et al also presented a covid-related tool called StayHome, a reusable mobile application to gather Patient-reported outcomes (PROs). The app was designed to gather covid-19 symptoms and share them with health organizations. In order to maintain interoperability, the FHIR standard was used [37]. In the study of Rosenau et al, the potential of research ontology's automatic generation by a terminology server and FHIR profiles was analyzed in the context of covid-19; the researchers also investigated the process of user input translation to FHIR queries [28].

C) Cancer:

In the context of research in cancer clinical trials, FHIR-based pipelines can also be utilized in order to automatically populate CRFs. The EDC pipeline was developed in order to model colorectal cancer trials as a case study. By utilizing the pipeline, real-world trials can be supported using EHR data [25]. In the research conducted on cancer by Zong et al, the aim was to classify cancer types and forecast the cancers of unknown primaries. Thus, genetic data elements (from cancer patients' oncology reports) and the related phenotyping data (from Mayo Clinic's EHR) were extracted for this study. The researchers then modeled the EHR and genetic data with FHIR. Machine learning techniques were also employed and compared to analyze the performance of cancer prediction models [29]. In another study in the context of cancer (colorectal), the aim was to model cancer CTs through FHIR. The presented methodology extensively captures the required data elements of CTs by CRFs. The information was then mapped to an equivalent element in the FHIR cancer profile [32]. In the article of Hong et al, an interactive statistics and analysis platform called Shiny FHIR was implemented for cancer (ovarian). The system encompasses related R packages, FHIR resources, and Shiny (a web app framework). [33].

D) Random and General Notes:

The NLP2FHIR pipeline can be used to make unstructured EHR data consistent and integrate it with structured data. This procedure will facilitate portable EHR-driven phenotyping and large-scale data-driven analytics. Hong et al attempted to assess the modeling capabilities of FHIR concentrating on core clinical resources by using unstructured data from Mayo Clinic EHR[16]. In another research, a framework was also designed in order to integrate unstructured and structured data into an interoperable format through implementing the NLP-based pipeline by the utilization of the FHIR type system. The Mayo Clinic's medication data was also used in this research [17]. The aim of Hong et al's study was to develop a framework for standardizing heterogeneous annotation corpora by FHIR specifications. The system includes two main modules (automatic schema mapping module and expert-based annotation and verification module) [19]. De et al presented a data model in the context of patient secure messages based on FHIR concepts (related to base, foundation, clinical, and financial) in order to define important and significant information contained in these sources. After annotating the sentences and creating a huge corpus, they extracted hidden topics related to three microconcepts (Fatigue, Patient visit, and Prednisone as highly-discussed topics) by conducting topic modeling [38].

E) Intensive Care:

In the field of intensive care, Bennett et al dealt with converting the MIMIC-IV database to FHIR. The MIMIC-IV dataset encompasses patient data from intensive care departments. To support the use of MIMIC-IV on FHIR, a resource demo, and a FHIR IG were also created [30]. A FHIR data harmonization pipeline (FHIR-DHP) was developed by Williams et al based on the ETL framework. They utilized five phases to harmonize EHR data; querying from the hospital database, mapping the retrieved data to FHIR format, mapping validation, transferring the FHIR resources to the patient-model database, and exporting data to JSON format. Consequently, raw clinical records could be transformed into AI-friendly and harmonized representations of data. This research also used the MIMIC-IV dataset for framework evaluation [18].

One article was about the maternal healthcare domain; a data access model based on RESTful web services was implemented by Ismail et al to maintain related data as FHIR resources to increase interoperability [35].

3.1.2 Non-Linear Data Models

These models **do not follow** a sequential or linear flow of data processing and instead they capture and integrate data in broader aspects and focus on the structure and representation of healthcare data or presenting a mapping model. In other words, these models are more likely to focus on capturing relationships between variables without strict dependencies on the ordering. Out of 26 included articles, 6 studies were related to the development of non-linear data models using the FHIR standard. Table 4 summarizes the important information and summary of the articles that presented these data models.

Table 4: Non-linear / mapping models

Authors	FHIR resources/elements used	Data source	Data transformation and mapping	Standards, tools, terminologies, models	Validation, evaluation	Use cases, applications

Continued on next page

Table 4 – continued from previous page

Authors	FHIR resources/elements used	Data source	Data transformation and mapping	Standards, tools, terminologies, models	Validation, evaluation	Use cases, applications
González-Castro et al [8]	Observation, Device, Questionnaire, QuestionnaireResponse, FamilyMemberHistory, AllergyIntolerance, Patient, Procedure, MedicationStatement, Condition, Encounter	patient medical records, PGD	map data elements to FHIR resources	SNOMED, LOINC	mapping possibilities check	cancer survivorship (colon and breast cancers)
Kukhareva et al et al [39]	Patient, Encounter, Observation, Procedure, *ProcedureRequest, RelatedPerson	Epic EHR	local codes to LOINC, local codes to standard codes, QUICK to different FHIR versions and profiles	EHR web services, FHIR services, Authorization services, SMART on FHIR, native EHR FHIR APIs, SNOMED, LOINC	feasibility check by clinicians	neonatal bilirubin management
Montazeri et al [40]	Patient, Observation, Condition, Medication, ServiceRequest, Practitioner	CPOE systems, Shafa hospital (Kerman, Iran)	data elements to FHIR	FHIR standard	Expert panel	Cardiovascular
Shivers et al [41]	AllergyIntolerance, Appointment, CarePlan, Communication, Condition, Consent, Coverage, *DeviceUseStatement, Encounter, HealthCareService, Medication, MedicationAdministration, MedicationStatement, Observation, Patient, Practitioner, Procedure, ServiceRequest	DAK data dictionaries that contain core data elements for recommendations about FP and STI	data mappings to FHIR and semantic terminologies (ICD-10, SNOMED-CT, LOINC, RxNorm)	ICD-10, SNOMED-CT, LOINC, RxNorm, IG, UMLS, IPS	iterative validation of mappings to identify discrepancies gaps, and errors	FP and STI
Lambarki et al [42]	Patient, Organization, Condition, ClinicalImpression, ServiceRequest, Encounter, Observation, Procedure, MedicationRequest	DKTK	FHIR data elements to corresponding ADT and ISO standard (11179-3 fields)	ICD-10, ICD-O-3, TNM, Forge, Simplifier, FHIR-validator, clinFHIR, LOINC, ADT/GEKID schema, OID	FHIR validator to validate FHIR profiles	oncology
Lichtner et al [43]	Composition, EvidenceVariable, PlanDefinition, ActivityDefinition, Citation, ArtifactAssessment, Evidence, Group	requirements engineering (COVID-19 evidence ecosystem (CEOsys) project members)	model's items to FHIR resources, information model to EBMonFHIR resources	EBMonFHIR, CPG-on-FHIR, FSH, SUSHI, HL7 FHIR IG Publisher tool, FHIR core artifacts, GRADE EtD framework, PICO framework, Cochrane PICO ontology, SNOMED CT, LOINC, ICD-10, ATC, UCUM, CEOsys, FEvIR platform	implementation of a recent COVID-19 guideline recommendation to evaluate EBMonFHIR-based guideline representation	Evidence-based CPG recommendations, COVID-19 intensive care patients guideline (evaluation phase)

** See Table 4 for the previously mentioned abbreviations.
Abbreviations: PGD: Patient-Generated Data, **QUICK:** Quality Improvement and Clinical Knowledge, **API:** Application Programming Interface, **CPOE:** Computerised Physician Order Entry, **DAK:** Digital Adaptation Kits, **FP:** Family Planning, **STI:** Sexually Transmitted Infections **IG:** Implementation Guide, **UMLS:** Unified Medical Language System, **IPS:** International Patient Summary, **DKTK:** German Cancer Consortium, **ADT:** Admission, Discharge, Transfer, **ICD-O:** International Classification of Diseases for Oncology, **TNM:** Tumour, Node, Metastasis, **OID:** Object Identifier, **EBM:** Evidence-Based Medicine, **CPG:** Clinical Practice Guideline, **SUSHI:** SUSHI Unshortens Short Hand Inputs, **GRADE EtD:** GRADE (Grading of Recommendations Assessment, Development and Evaluation) Evidence to Decision, **UCUM:** Unified Code for Units of Measure, **FEvIR:** Fast Evidence Interoperability Resources,

Non-linear data models mainly deal with mapping data elements to FHIR resources and presenting a model on how the resources can be mapped and related together. Since the number of articles in this category was low, we summarized all of them in one section (clinical-based).

In the study of González-Castro et al, an interoperable data model called CASIDE was developed in the context of cancer survivorship. The researchers defined data elements and then mapped them in the corresponding FHIR resources. The patient information was illustrated through the collection of FHIR resources including "condition, Observation, MedicationStatement, Encounter, Procedure" [8]. Kukhara et al developed an application for the management of bilirubin in neonates. The app also included custom FHIR interfaces. Several strategies were investigated to modify the app for cross-institutional transmission after extensive intra-institutional use. The app's adaptation for cross-institutional dissemination involves clinician-specific implementation by using custom FHIR APIs, user feedback gathering, differential features based on FHIR capabilities, implementing progressive replacement with native FHIR interfaces, and using the "QUICK" logical data model for mapping to different FHIR versions and profiles [39]. Lambarki et al presented a harmonized data model based on FHIR in the context of cancer research. German cancer care providers are required to report patient data to cancer registries using a specific schema called ADT/GEKID. For this reason, The XML representation was compared to the extended version in DKTK, and a codification of the cancer life cycle was created. The DKTK data model was represented using FHIR and the FGIR resources were identified. Other oncology FHIR profiling endeavors were analyzed for reuse in DKTK. Tools used for implementing FHIR profiles included Forge (a desktop application for tailoring resources to specific profiles), Simplifier (a FHIR registry for hosting profiles), and FHIR validator to validate profiles [42]. Montazeri et al presented a multi-method approach containing the development of an MDS for cardiovascular CPOE. The researchers identified and classified critical data elements by reviewing medical records contents and then mapped them to the FHIR standard [40]. In the study of Shivers et al, the domains of medicine were family planning and sexually transmitted interventions. The researchers initially structured data dictionaries to enhance the mapping procedures to FHIR, ICD-10, LOINC, SNOMED-CT, and RxNorm. Then the corresponding FHIR resources and codes were identified and assigned to each data dictionary term. The ultimate objective was to prepare inputs - in this case, mappings and data dictionary - for an IG generation tool [41]. In the research conducted by Lichtner et al, The objective was to outline a technique for providing FHIR-based evidence-based CPG recommendations. Iterative consensus-based mapping of the model's items and connections to FHIR correspondences was covered in the research along with modeling of the recommendations. According to the CPG-on-FHIR framework, the generated guideline recommendations were represented using FHIR profiles [43].

3.2 Technical Approaches

With respect to developing data models or infrastructures using the FHIR standard, some tools were utilized in all reviewed research articles. In this section, important tools and approaches that need to be declared in addition to the tables, will be discussed (RQ4).

3.2.1 FHIR-based Tools and Frameworks

A) NLP2FHIR: Several studies (mainly in the first category 3.1.1), employed NLP tools as part of the data model's implementation. NLP2FHIR pipeline was used in [15, 16, 24, 29]. This pipeline is the FHIR-based clinical data normalization pipeline that can be used for EHR-driven phenotyping. As shown in Fig. 2, this pipeline gets the EHR data in every possible format (structured, semi-structured, and unstructured) as input to the pipeline. In the pipeline itself, the FHIR type system, as well as NLP tools, are utilized. The required binaries to execute this pipeline are as follows: MedTagger, cTAKES, MedTime, MedXN, UMLS VTS. The raw clinical data is then transformed into FHIR bundles. The FHIR-based data will be easily integrated into EHR systems. Eventually, phenotypes can be created based on FHIR bundles [44].

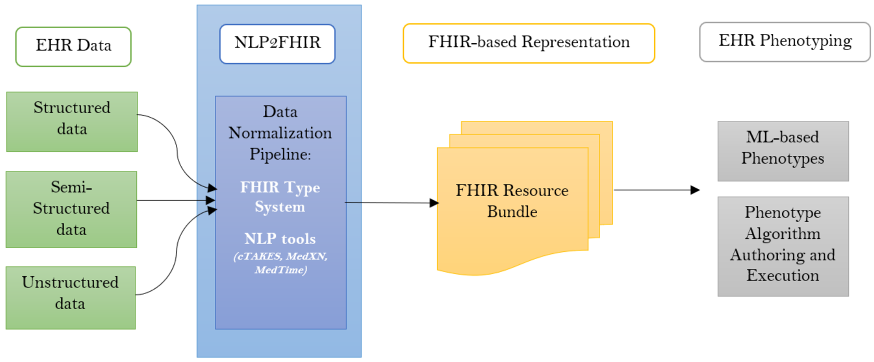

Fig. 2: NLP2FHIR Data Normalization Pipeline and its applications

To elaborate more, by using this pipeline, the data included in discharge summaries can be transformed into FHIR resources [15]. In addition, normalization and mapping rules, as well as NLP-based FHIR extensions can be implemented through NLP2FHIR and it is proved that this pipeline can be a practical tool for modeling unstructured data in order to eventually integrate the structured elements to models [16]. Wen et al integrated an NLP ruleset generation process into this pipeline [24]. Family history records were processed by NLP2FHIR in Zong et al's study [29].

B) SMART-on-FHIR: This specification can be used for data and security requirements for health-related applications. A workflow of secure requests for data access as well as receiving and using that data is defined by SMART-on-FHIR [45]. In other words, this specification is a framework containing web standards that are utilized to define health applications based on the FHIR server's data. Marteau et al developed a SMART on FHIR app containing a query and upload page. [34].

Kukhareva et al assessed the balancing functionality and portability of SMART on FHIR apps in the context of neonatal bilirubin management [39].

C) EBM-on-FHIR and CPG-on-FHIR: EBM-on-FHIR is a knowledge assets project about FHIR resources for Evidence-Based Medicine (EBM). The objective of EBM-on-FHIR is to offer interoperability for individuals who produce, analyze, synthesize, disseminate, and implement clinical evidence and clinical practice guidelines [46]. CPG-on-FHIR is an IG for FHIR clinical guidelines for using FHIR resources in building computable and interoperable representations of clinical care guidelines' contents [47]. Lichtner et al developed an IG that utilized the resources designed by EBM-on-FHIR to represent primary evidence and the process of "evidence to decision". These resources were eventually integrated into the CPG-on-FHIR framework. Both EBM-on-FHIR and CPG-on-FHIR are supported by the HL7 CDS workforce and represent diverse aspects of evidence-based guideline recommendations. The former concentrates on the justification aspects of the recommendations, while the latter concentrates on the implementation aspects of the recommendations [43].

D) clinFHIR: clinFHIR is an online open-source educational environment that also provides the possibility for developers to create or search FHIR-based resources [48]. Guinez-Molinos et al utilized clinFHIR graphBuilder to model the relationships between resources. This tool also assembles resource instances into a graph with related resources to specify a scenario using FHIR [36]. The structure of the model presented by Lambarki et al was also visualized using clinFHIR software [42].

E) HAPI FHIR: HAPI FHIR is a comprehensive implementation of FHIR in Java language [49]. This API is for both FHIR clients and servers [50]. Several studies utilized this API in the data model implementation process. Bennett et al utilized the HAPI FHIR server in the process of validation, for bulk exporting and writing data to NDJSON files [30]. Hong et al used this API to put ovarian cancer data into FHIR resources (Patient. Observation, Condition, Procedure). They also employed HAPI FHIR client API to upload structured FHIR data elements to the FHIR server. HAPI was one of the testing servers that was used to assess data quality and server stability [33]. This API can also be used in the NLP domain. Hong et al used HAPI FHIR for annotation serialization; they converted the annotations into FHIR XML and JSON formats that would eventually be represented in a FHIR-consistent format. HAPI FHIR resource validator API was also used to validate the resources to be compliant with FHIR specification [19]. In the model presented by Guinez-Molinos et al, HAPI FHIR database was used to store resources. HAPI server version 5.1 was responsible for the interoperability layer of the model [36]. For persistent data storage and a FHIR server, Burkhardt et al utilized HAPI FHIR V4.2.0 [37].

3.2.2 Machine Learning Approaches

Aside from the utilization of NLP2FHIR discussed in 3.2.1(A), some other articles solely made use of NLP tools and algorithms to convert unstructured data to structured data elements [25]. Hong et al utilized UIMA NLP tools such as MedXN and MedTime in the normalization phase to increase interoperability. MedXN was employed for medication concept extraction and MedTime was employed for FHIR-defined temporal elements. Separate NLP extraction modules were developed in an attempt to directly extract from free-text, for the entities that cannot be extracted by present NLP tools [17]. In a classification system developed by Hong et al, four machine learning algorithms including the Support Vector Machine, random forest, logistic regression, and decision tree were implemented for training the classifiers; the features that were used by the system were extracted from FHIR resources as well as terminology expansions [15]. Zong et al analyzed some deep learning and machine learning backbone models to compare the performance of cancer prediction. Bag of features (or bag of words) was used in their research based on the values of attributes in the FHIR model. A graph embedding methodology, called Node2vec, was utilized in order to learn the patients' (a vector) features. In general, three methods of feature generation were compared, including bag of features, Node2vec, and bag of features combined with Node2vec. Moreover, seven classification algorithms were analyzed and compared (random forest, logistic regression, naive Bayes, deep neural network, support vector machine, graph convolutional network, and convolutional neural network) [29]. In the data model presented by Zong et al, NLP tools were used to provide structured data for the ELT process from unstructured data (such as surgical reports). To cluster each patient in the process of patient subgrouping, they Utilized a topic model called Dirichlet Multinomial Mixture (DMM) for one topic per document [32]. The genetic relation extractor developed by Hong et al used Support Vector Machine as a learning model; the aim was to extract the element called "FamilyMemberHistory.relationship". Eventually, the pooled corpora's NLP performance was demonstrated [19]. To learn the hidden topics of patient messages, De et al, utilized the Latent Dirichlet allocation (LDA)- an unsupervised topic learning model [38].

3.2.3 Data Storage and Security

Multiple studies used PostgreSQL (also known as Postgres) as the database management system (DBMS) [18, 30, 34, 37]. This system is an SQL-based open-source relational DBMS that is compatible with JSON document storage. In the study of Williams et al, data storage was based on FHIR resource type, and each resource is assigned to a separate JSON structure [18]. Bennett et al used the Medical Information Mart for Intensive Care (MIMIC)-IV database; the data contained in this data source was loaded into Postgres. They then mapped the elements into JSON within this system [30]. To store the converted "OMOP CDM database", Marteau et al used the Postgres system [34]. Burkhardt et al also used this system in their proposed architecture [37]. On the other hand, Ismail et al utilized MongoDB (NoSQL or non-relational data storage) for data record manipulation processes [35]. For authorization, some researchers used OAuth [31] and Keycloak [37]. For security (authentication), Javascript Object Notation (JWT) [36, 37] was used in some studies.

3.3 Limitations and Challenges

Designing data models can bring about many challenges and limitations due to the issues about data integration, interoperability, standardization, performance, scalability, and many more. This section deals with some of these challenges and limitations for the researchers to develop FHIR-based data models (RQ6). It should be mentioned that in the limitation aspects, there are some issues with the final product or data model that the authors need to consider in future research or mention as a recommendation for other researchers. While in the aspects of the challenges, the scientists faced some difficulties during the implementation and they were likely to be resolved in the discussed research itself. Table 5 summarizes these items reported in the reviewed studies that can be categorized into/lead to these challenges. It should be mentioned that some items may be assigned to more than one category. Based on the results, most challenges are related to data integration and standardization.

- **Data integration** is the process of combining data from multiple sources and creating a unified set of data. The initial stage in working on data analytics, reporting, and forecasting is data integration [51]. The issues dealing with this kind of process are shown in the data integration category.
- **Interoperability** issues are related to the limitations in the seamless transfer and exchange of information between medical systems or applications [52].
- **Data Standardization** is a crucial step in transforming data into a uniform format in order to enable the shared use of advanced tools and techniques, large-scale analytics, and collaborative research [53]. Therefore, standardization issues are related to challenges in attaining standard and consistent representation of data across different medical systems.
- **Performance** issues are related to obstacles in the efficient processing and retrieval of data which can compromise system performance; for example, the data is not processed within an acceptable response time [54].
- **Scalability** limitations can be considered as the data model's weakness in handling increasing data volume or workload. **Generalizability** problems are the challenges in the applicability of the data model to other aspects or settings.

3.4 Scientometric/bibliometric Analyses

3.4.1 Word Cloud

In this section, we will demonstrate the keyword analysis of the selected articles. We employed word cloud generator [55] to analyze the keywords section of the 26 included articles (Fig. 3). It should be mentioned that, we concatenated the words of two- or three-word keywords together since we believed they were related and should be shown as one concept (for instance for Medical Informatics, it was shown as MedicalInformatics).

3.4.2 Resource Frequencies

According to the FHIR resource list and official categorization [9], there are five FHIR resource categories including **Foundation, Base, Clinical, Financial, and**

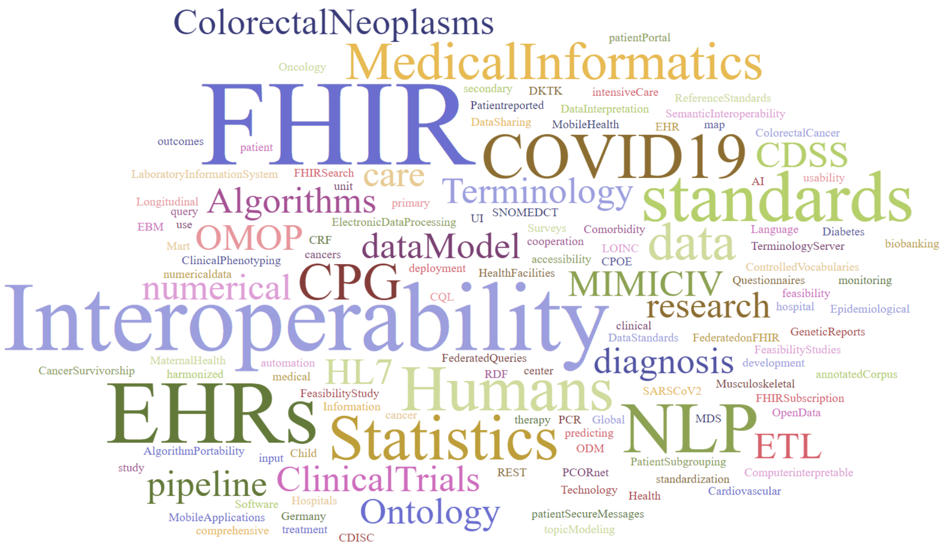

Fig. 3: Keyword analysis using Wordcloud for the systematic review

Specialized. Based on the results from extracted articles, the resources from the "Clinical" category were used 95 times followed by the "Base" category (36 times). "Foundation" and "Specialized" each had six resources and from the "Financial" category, only one resource was used. It is worth noting that some resources were used more than once.

Fig 4 illustrates the frequency of each resource in all included articles (RQ5). It should be mentioned that in this section, we only discuss FHIR resources, and some elements such as "BodySite" which is part of some resources like "Observation" and "Condition" will not be illustrated here. In addition, in the study of De et al [38], some FHIR definitions were not included in the FHIR resource list of R5 such as "*LabTest, Imaging, Referral, Risk, CoverageEligibility, ClaimPayment*". Therefore, we did not include them in our visualization analysis (same for ProcedureRequest in [39], Dosage in [31], and DeviceUseStatement in [41]).

As is shown in the figure, in 19 articles, the "Observation" resource was used, followed by "Patient" and "Condition" resources each in 16 research articles. The figure highlights the resources that were used in 3 or more articles. The other resources and their frequencies are as follows:

'AdverseEvent', 'Appointment', 'Communication', 'Consent', HealthCareService, 'Immunization', 'ValueSet': Frequency=2

'Account', 'ActivityDefinition', 'ArtifactAssessment', 'BodyStructure', 'CareTeam', 'Citation', 'ClinicalImpression', 'CodeSystem', 'Coverage', 'DocumentReference', 'EpisodeOfCare', 'Evidence', 'EvidenceVariable', 'ExplanationOfBenefit', 'Goal', 'Group', 'Location', 'NutritionOrder', 'PlanDefinition': Frequency=1

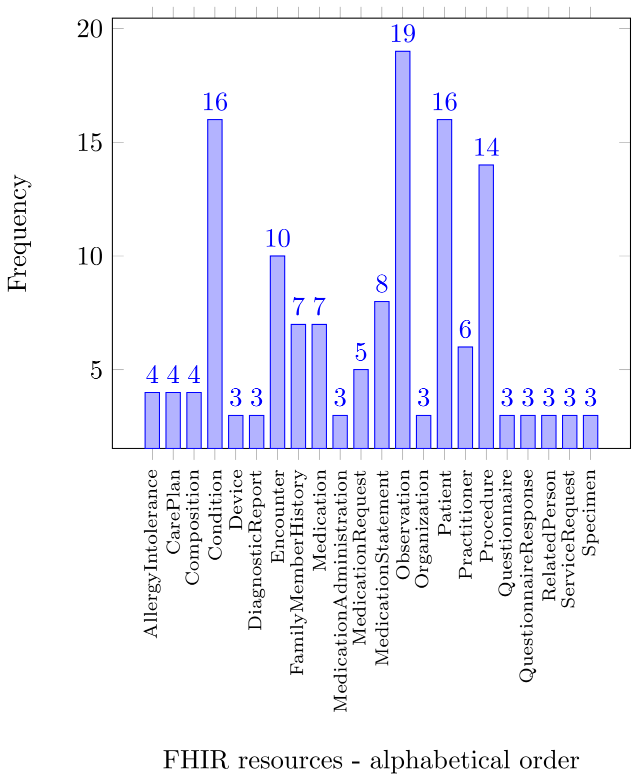

Fig. 4: Frequency of FHIR Resources in the Included Articles

3.4.3 Distribution by year

Fig. 5 illustrates the distribution of included studies considering the year they were published. As shown in the figure, the year 2021 encompasses the highest number of publications (10 articles) while in 2016 there was only one article.

3.5 Proposed Architecture

Based on the knowledge obtained from reading the previous articles, we can propose a model that utilizes the FHIR standard to increase interoperability among multiple healthcare systems (RQ7). Fig 6 illustrates the architecture in which data from multiple sources are first integrated into a data warehouse with the utilization of ELT processes. The integrated data will be checked for conformance (value, relational, computational), completeness, and plausibility (uniqueness, atemporal, temporal) in a so-called process of data quality check as proposed by Kahn et al [56] and used in the proposed architecture of data quality API by Spengler et al [57]. The API proposed in their research can be an ideal example to use in the data models. The output of this phase will be visualized for data monitoring by Grafana software. In the next

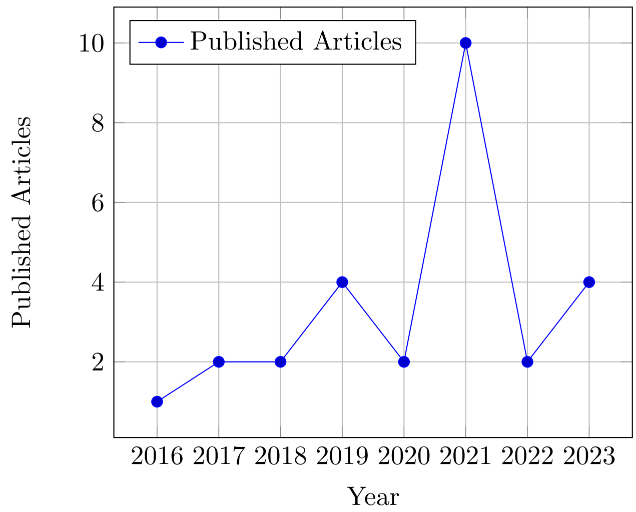

Fig. 5: Published Articles per Year

step, FHIR resources and their relationships and dependencies will be defined and in the next phase, the FHIR IG will be developed.

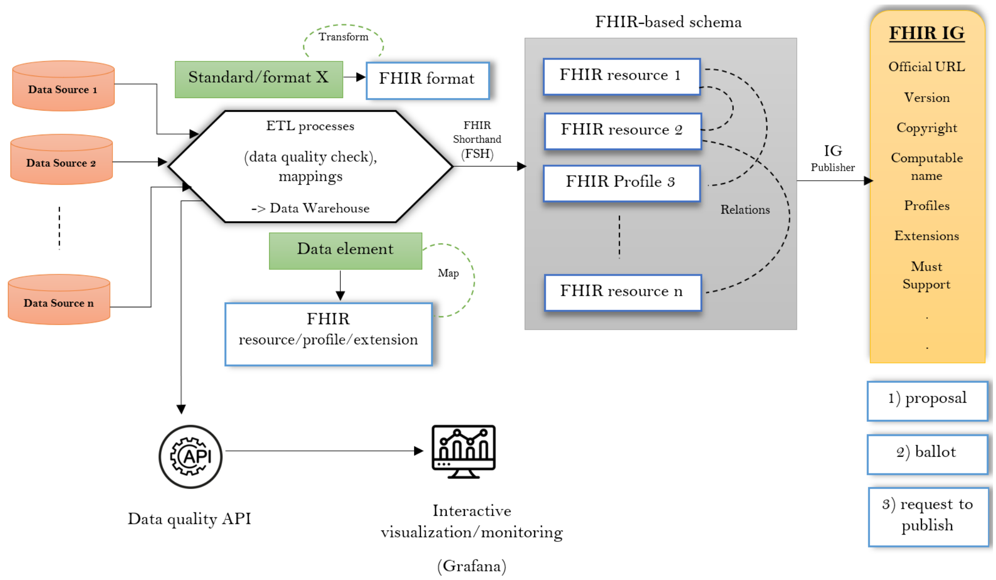

Fig. 6: FHIR-based modeling process

4 Discussion

In this review, we aimed to provide an overview of the best practices in the context of developing FHIR-based data models. We summarized each included article and extracted information about the FHIR resources, technologies and standards, and mappings. It was additionally aimed to extract and summarize the limitations of each research in an attempt to provide a comprehensive view of the potential challenges and limitations that future researchers may face and try to be prepared.

*** Enhance discussion ** Everything we write would be duplicates of results

4.1 Related Works: *Review of Reviews*

In order to comprehensively compare this study with similar reviews about FHIR, we conducted a separate search in the PubMed database using "FHIR" OR "Fast Healthcare Interoperability Resources" with "Review" OR "Systematic Review" filter. This search retrieved 41 results with no time limit. We identified seven review articles about FHIR among the retrieved studies.

As far as our research highlights, no reviews were published focusing specifically on the FHIR standard in data models or FHIR-based data infrastructures/architectures. However, there are some valuable review studies considering other aspects of the FHIR standard. A study by Ayaz et al [58] in 2021, which can be the most similar study to ours, reviewed all aspects of FHIR in the articles published from January 2012 to December 2019. Our study included more recent articles from 2020 to 2023 too. The main aim of their study was to analyze the articles according to implementation, challenges, future applications, and opportunities of this standard. The researchers reviewed the articles which focused on all categories including apps, SMART, FHIR implementation models, FHIR resources, FHIR framework, mapping framework/data model, challenges, and FHIR goals. Our study reviewed articles that only focused on FHIR data models or infrastructures. The researchers also summarized the resources used in the included articles; "Observation" and "Patient" resources respectively were the most-used resources in the included articles. We similarly performed this analysis and had close results; as we mentioned earlier in our study, "Observation" followed by ("Patient" and "Condition") resources were used more often. The mentioned researchers also discussed the mapping approaches from other techniques or methods to FHIR. In our study, we summarized all the techniques, tools, and standards used in the FHIR data models.

The focus of Vorisek et al's study [59] was to review the FHIR standard from the "health research" point of view. The researchers analyzed the studies that utilized FHIR in every aspect of the research process such as data capture, recruitment, data standardization, analysis, and consent management. Moreover, they categorized the articles with generic or specific clinical specialty approaches. We also categorized our articles based on the medical field. In the mentioned research, it was reported that most studies utilized other terminologies and data models aside from FHIR; they included SNOMED-CT, LOINC, ICD-10, OMOP-CDM, and more. It was reported that among "data capture-related" studies, the "Questionnaire" resource was used more often, as expected. In addition to scientific aspects, the limitations of using

FHIR were discussed, similar to our research. They highlighted that the limitations may include evolving FHIR resources' contents, legal issues, safety, and the necessity to have FHIR server. In our study, on the other hand, we categorized the limitations into the aspects of data integration, interoperability, standardization, performance, and scalability/generalizability. Concerning medical research aspects of FHIR, Duda et al [60] also presented a literature review in 2022. This study used the "expanded Marquis-Gravel categories" in which it is possible to categorize the way every project contributes to research tasks. The researchers reviewed FHIR projects focusing on research which included preparation (e.g., mapping to/from FHIR), pre-study (e.g., define/refine cohort), study setup (e.g., data collection for research), recruitment (e.g., including screening criteria in EHR), study conduct (e.g., patient data collection), and post-study (e.g., data sharing). "General research preparation" was the focus of most projects (such as infrastructure and data pipeline development). Lehne et al [61] reviewed the application of FHIR in digital health. Based on their research, the reviewed articles were mostly related to data models, mobile/web applications, and medical devices.

Some other articles reviewed interoperability and data exchange standards. In the research conducted by Schweitzer et al [62] in 2022, the researchers narratively described and compared exchange approaches such as DICOM, Integrating the Healthcare Enterprise (IHE) initiative, and clinical terminologies (such as SNOMED-CT) as well as FHIR in the field of teleophthalmology. The researchers mentioned the ophthalmology-related FHIR resource which is "VisionPrescription" as well as the current proposal of the related IG. Torab-Miandoab et al [63] reviewed interoperability approaches and requirements for semantics interoperability between heterogeneous health information systems. It was stated that FHIR, CDA, SOA, RIM, HIPPA security standard, SNOMED-CT, XML, JAVA, SQL, and API can be considered the most crucial requirements to implement semantic interoperability. The summary of interoperability standards in the contexts of terminology, content, transport, and security was presented as well based on the results. The researchers also highlighted the categorization of interoperability architectures components with the main categories of service-oriented architecture, archetype-based, web-based, client-server, multi-agent, blockchain-based, XML-based, cloud-based, ontology-based, object-oriented, and local network. Yogesh and Karthikeyan [64] reviewed FHIR architectural specifications such as the linkages, workflow state, healthcare informatics, and public health safety approaches using this standard. The researchers also highlighted the probable challenges with healthcare data standards including, coding speed and accuracy problems, code mappings, compatibility issues between new and legacy systems, and communication concerns between EHRs and patients. Some issues of the standards presented in this research confirm the results of our review with respect to the challenges of utilizing healthcare standards when developing a data model or infrastructure.

4.2 Key Findings

The most used resources were from the "Clinical" category of FHIR resources. The reason behind selecting clinical resources for developing data models may be because of the fact that we included articles with the practical data model for a clinical disease or complication (or a series of conditions) and we were not eager to discuss the general data models. Therefore, in these articles, the most-used FHIR resources were from the "Clinical" category. From the limitations point of view, several articles addressed the issues related to data integration and standardization.

4.3 Future Directions and Recommendations

During conducting this study, we came across some ideas and recommendations for future research including 1) the comparison of other models and FHIR. The models may include but are not restricted to SNOMED-CT, previous versions of HL7 interoperability standards (e.g. HL7-V2, CDA), OpenEHR, and OMOP and elaborate on the models created with these standards, focusing on the methodological aspects, limitations, strengths, and interoperability maintenance, 2) highlighting the ontological aspects of data models, and discussing how they represent medical terminologies and concepts.

4.4 Research Limitations

This research has some limitations. *First of all*, we focused on only the articles that dealt with a specific disease and we excluded the ones with general proposed or developed data models. In this case, we may have some generalizability issues or biases, especially with respect to the resources used and methodologies and also with ontological data models. *Second*, we did not analyze published articles other than in the English language, therefore we may have missed some research due to this inclusion criteria. *Third*, since we did not thoroughly analyze the grey literature, we may have missed some research studies.

5 Conclusion

Based on the results of our review, the FHIR data models can be a very promising interoperability standard. Policymakers and healthcare specialists can utilize this standard in any field such as healthcare, research, administration, finance, and so on. Additionally, when developing data models, this standard can also be integrated with other health-related standards in an attempt to propose a more interoperable solution.

Supplementary information.

Acknowledgments.

Declarations

- Funding:
  This research is partially funded by grant number X from the Department of Informatics at the University of Salerno, Italy.
- Conflict of interest/Competing interests:
  Non-declared.
- Ethics approval:
  Not applicable.

- Availability of data and materials:
  Not applicable.
- Code availability:
  Not applicable.
- Authors' contributions:
  All authors contributed equally to this work.

Appendix A Section title of first appendix

An appendix contains ...

References

[1] Carvalho, G., Mykolyshyn, S., Cabral, B., Bernardino, J., Pereira, V.: Comparative analysis of data modeling design tools. IEEE Access **10**, 3351–3365 (2021)

[2] Kahn, M.G., Batson, D., Schilling, L.M.: Data model considerations for clinical effectiveness researchers. Medical care **50** (2012)

[3] Danese, M.D., Halperin, M., Duryea, J., Duryea, R.: The generalized data model for clinical research. BMC medical informatics and decision making **19**(1), 1–13 (2019)

[4] Lehne, M., Sass, J., Essenwanger, A., Schepers, J., Thun, S.: Why digital medicine depends on interoperability. npj Digit. Med **2**(1) (2019)

[5] Stan, O., Miclea, L.: Local ehr management based on fhir. In: 2018 IEEE International Conference on Automation, Quality and Testing, Robotics (AQTR), pp. 1–5 (2018). IEEE

[6] Borisov, V., Minin, A., Basko, V., Syskov, A.: Fhir data model for intelligent multimodal interface. In: 2018 26th Telecommunications Forum (TELFOR), pp. 420–425 (2018). IEEE

[7] Noumeir, R.: Active learning of the hl7 medical standard. Journal of digital imaging **32**(3), 354–361 (2019)

[8] González-Castro, L., Cal-González, V.M., Del Fiol, G., López-Nores, M.: Caside: A data model for interoperable cancer survivorship information based on fhir. Journal of Biomedical Informatics **124**, 103953 (2021)

[9] FHIR Fact Sheets. https://www.healthit.gov/topic/standards-technology/standards/fhir-fact-sheets. Accessed: 2023-06-05

[10] FHIR Extensibility and Profiling. http://hl7.org/fhir/overview-clinical.html. Accessed: 2023-07-24

[11] FHIR Bundle. https://build.fhir.org/bundle.html. Accessed: 2023-07-24

[12] FHIR Code systems and Value sets. http://hl7.org/fhir/codesystem.html. Accessed: 2023-07-24

[13] FHIR Implementation Guide. https://www.hl7.org/fhir/implementationguide.html. Accessed: 2023-07-24

[14] Lenert, L.A., Ilatovskiy, A.V., Agnew, J., Rudisill, P., Jacobs, J., Weatherston, D., Deans Jr, K.R.: Automated production of research data marts from a canonical fast healthcare interoperability resource data repository: applications to covid-19 research. Journal of the American Medical Informatics Association **28**(8), 1605–1611 (2021)

[15] Hong, N., Wen, A., Stone, D.J., Tsuji, S., Kingsbury, P.R., Rasmussen, L.V., Pacheco, J.A., Adekkanattu, P., Wang, F., Luo, Y., *et al.*: Developing a fhir-based ehr phenotyping framework: A case study for identification of patients with obesity and multiple comorbidities from discharge summaries. Journal of biomedical informatics **99**, 103310 (2019)

[16] Hong, N., Wen, A., Shen, F., Sohn, S., Wang, C., Liu, H., Jiang, G.: Developing a scalable fhir-based clinical data normalization pipeline for standardizing and integrating unstructured and structured electronic health record data. JAMIA open **2**(4), 570–579 (2019)

[17] Hong, N., Wen, A., Shen, F., Sohn, S., Liu, S., Liu, H., Jiang, G.: Integrating structured and unstructured ehr data using an fhir-based type system: a case study with medication data. AMIA Summits on Translational Science Proceedings **2018**, 74 (2018)

[18] Williams, E., Kienast, M., Medawar, E., Reinelt, J., Merola, A., Klopfenstein, S.A.I., Flint, A.R., Heeren, P., Poncette, A.-S., Balzer, F., *et al.*: A standardized clinical data harmonization pipeline for scalable ai application deployment (fhir-dhp): Validation and usability study. JMIR Medical Informatics **11**, 43847 (2023)

[19] Hong, N., Wen, A., Mojarad, M.R., Sohn, S., Liu, H., Jiang, G.: Standardizing heterogeneous annotation corpora using hl7 fhir for facilitating their reuse and integration in clinical nlp. In: AMIA Annual Symposium Proceedings, vol. 2018, p. 574 (2018). American Medical Informatics Association

[20] Carrera-Rivera, A., Ochoa-Agurto, W., Larrinaga, F., Lasa, G.: How-to conduct a systematic literature review: A quick guide for computer science research. MethodsX, 101895 (2022)

[21] Booth, A., Sutton, A., Papaioannou, D.: Systematic Approaches to a Successful Literature Review. Sage, London (2016). © 2016 Andrew Booth, Anthea Sutton and Diana Papaioannou. https://eprints.whiterose.ac.uk/105755/

[22] PRISMA Flow Diagram. http://prisma-statement.org/prismastatement/flowdiagram.aspx?AspxAutoDetectCookieSupport=1. Accessed: 2023-09-12

[23] Raj, A., Bosch, J., Olsson, H.H., Wang, T.J.: Modelling data pipelines. In: 2020 46th Euromicro Conference on Software Engineering and Advanced Applications (SEAA), pp. 13–20 (2020). IEEE

[24] Wen, A., Rasmussen, L.V., Stone, D., Liu, S., Kiefer, R., Adekkanattu, P., Brandt, P.S., Pacheco, J.A., Luo, Y., Wang, F., *et al.*: Cql4nlp: development and integration of fhir nlp extensions in clinical quality language for ehr-driven phenotyping. AMIA Summits on Translational Science Proceedings **2021**, 624 (2021)

[25] Zong, N., Wen, A., Stone, D.J., Sharma, D.K., Wang, C., Yu, Y., Liu, H., Shi, Q., Jiang, G.: Developing an fhir-based computational pipeline for automatic population of case report forms for colorectal cancer clinical trials using electronic health records. JCO Clinical Cancer Informatics **4**, 201–209 (2020)

[26] Fischer, P., Stöhr, M.R., Gall, H., Michel-Backofen, A., Majeed, R.W.: Data integration into omop cdm for heterogeneous clinical data collections via hl7 fhir bundles and xslt. In: Digital Personalized Health and Medicine, pp. 138–142. IOS Press, ??? (2020)

[27] Pfaff, E.R., Champion, J., Bradford, R.L., Clark, M., Xu, H., Fecho, K., Krishnamurthy, A., Cox, S., Chute, C.G., Overby Taylor, C., *et al.*: Fast healthcare interoperability resources (fhir) as a meta model to integrate common data models: development of a tool and quantitative validation study. JMIR medical informatics **7**(4), 15199 (2019)

[28] Rosenau, L., Majeed, R.W., Ingenerf, J., Kiel, A., Kroll, B., Köhler, T., Prokosch, H.-U., Gruendner, J.: Generation of a fast healthcare interoperability resources (fhir)-based ontology for federated feasibility queries in the context of covid-19: feasibility study. JMIR Medical Informatics **10**(4), 35789 (2022)

[29] Zong, N., Ngo, V., Stone, D.J., Wen, A., Zhao, Y., Yu, Y., Liu, S., Huang, M., Wang, C., Jiang, G., *et al.*: Leveraging genetic reports and electronic health records for the prediction of primary cancers: algorithm development and validation study. JMIR Medical Informatics **9**(5), 23586 (2021)

[30] Bennett, A.M., Ulrich, H., Damme, P., Wiedekopf, J., Johnson, A.E.: Mimic-iv on fhir: converting a decade of in-patient data into an exchangeable, interoperable format. Journal of the American Medical Informatics Association **30**(4), 718–725 (2023)

[31] El-Sappagh, S., Ali, F., Hendawi, A., Jang, J.-H., Kwak, K.-S.: A mobile health monitoring-and-treatment system based on integration of the ssn sensor ontology and the hl7 fhir standard. BMC medical informatics and decision making **19**(1), 1–36 (2019)

[32] Zong, N., Stone, D.J., Sharma, D.K., Wen, A., Wang, C., Yu, Y., Huang, M., Liu, S., Liu, H., Shi, Q., *et al.*: Modeling cancer clinical trials using hl7 fhir to support downstream applications: A case study with colorectal cancer data. International journal of medical informatics **145**, 104308 (2021)

[33] Hong, N., Prodduturi, N., Wang, C., Jiang, G.: Shiny fhir: an integrated framework leveraging shiny r and hl7 fhir to empower standards-based clinical data applications. Studies in health technology and informatics **245**, 868 (2017)

[34] Marteau, B.L., Zhu, Y., Giuste, F., Shi, W., Carpenter, A., Hilton, C., Wang, M.D.: Accelerating multi-site health informatics with streamlined data infrastructure using omop-on-fhir. In: 2022 44th Annual International Conference of the IEEE Engineering in Medicine & Biology Society (EMBC), pp. 4687–4690 (2022). IEEE

[35] Ismail, S., Alshmari, M., Qamar, U., Butt, W.H., Latif, K., Ahmad, H.F.: Hl7 fhir compliant data access model for maternal health information system. In: 2016 IEEE 16th International Conference on Bioinformatics and Bioengineering (BIBE), pp. 51–56 (2016). IEEE

[36] Guinez-Molinos, S., Andrade, J.M., Negrete, A.M., Vidal, S.E., Rios, E., *et al.*: Interoperable platform to report polymerase chain reaction sars-cov-2 tests from laboratories to the chilean government: Development and implementation study. JMIR Medical Informatics **9**(1), 25149 (2021)

[37] Burkhardt, H.A., Brandt, P.S., Lee, J.R., Karras, S.W., Bugni, P.F., Cvitkovic, I., Chen, A.Y., Lober, W.B.: Stayhome: a fhir-native mobile covid-19 symptom tracker and public health reporting tool. Online Journal of Public Health Informatics **13**(1) (2021)

[38] De, A., Huang, M., Feng, T., Yue, X., Yao, L.: Analyzing patient secure messages using a fast health care interoperability resources (fihr)–based data model: development and topic modeling study. Journal of medical Internet research **23**(7), 26770 (2021)

[39] Kukhareva, P., Warner, P., Rodriguez, S., Kramer, H., Weir, C., Nanjo, C., Shields, D., Kawamoto, K.: Balancing functionality versus portability for smart on fhir applications: case study for a neonatal bilirubin management application. In: AMIA Annual Symposium Proceedings, vol. 2019, p. 562 (2019). American Medical Informatics Association

[40] Montazeri, M., Khajouei, R., Mahdavi, A., Ahmadian, L.: Developing a minimum

data set for cardiovascular computerized physician order entry (cpoe) and mapping the data set to fhir: A multi-method approach. Journal of Medical Systems **47**(1), 1–13 (2023)

[41] Shivers, J., Amlung, J., Ratanaprayul, N., Rhodes, B., Biondich, P.: Enhancing narrative clinical guidance with computer-readable artifacts: Authoring fhir implementation guides based on who recommendations. Journal of Biomedical Informatics **122**, 103891 (2021)

[42] Lambarki, M., Kern, J., Croft, D., Engels, C., Deppenwiese, N., Kerscher, A., Kiel, A., Palm, S., Lablans, M.: Oncology on fhir: a data model for distributed cancer research. Stud Health Technol Inform **278**, 203–210 (2021)

[43] Lichtner, G., Alper, B.S., Jurth, C., Spies, C., Boeker, M., Meerpohl, J.J., Dincklage, F.: Representation of evidence-based clinical practice guideline recommendations on fhir. Journal of Biomedical Informatics **139**, 104305 (2023)

[44] NLP2FHIR Github. https://github.com/BD2KOnFHIR/NLP2FHIR. Accessed: 2023-09-04

[45] SMART on FHIR specification. https://tinyurl.com/brzcuuw2. Accessed: 2023-09-08

[46] EBM-on-FHIR confluence. https://confluence.hl7.org/display/CDS/EBMonFHIR. Accessed: 2023-09-05

[47] CPG-on-FHIR confluence. https://confluence.hl7.org/display/CDS/CPGonFHIR. Accessed: 2023-09-05

[48] ClinFHIR. https://ecqi.healthit.gov/tool/clinfhir. Accessed: 2023-09-05

[49] HAPI FHIR. https://hapifhir.io/. Accessed: 2023-09-05

[50] HAPI FHIR GitHub. https://github.com/hapifhir/hapi-fhir. Accessed: 2023-09-05

[51] Data Integration definition and challenges. https://www.datatobiz.com/blog/most-common-data-integration-challenges/. Accessed: 2023-07-04

[52] Data Interoperability. https://www.himss.org/resources/interoperability-healthcarehttps://www.ohdsi.org/data-standardization/. Accessed: 2023-07-05

[53] Data Standardization. https://www.ohdsi.org/data-standardization/. Accessed: 2023-07-05

[54] Performance Issues. https://www.ibm.com/docs/en/txseries/8.2?topic=troubleshooting-identifying-resolving-performance-issues. Accessed: 2023-09-18

[55] Word Cloud. https://www.jasondavies.com/wordcloud/

[56] Kahn, M.G., Callahan, T.J., Barnard, J., Bauck, A.E., Brown, J., Davidson, B.N., Estiri, H., Goerg, C., Holve, E., Johnson, S.G., et al.: A harmonized data quality assessment terminology and framework for the secondary use of electronic health record data. Egems **4**(1) (2016)

[57] Spengler, H., Gatz, I., Kohlmayer, F., Kuhn, K.A., Prasser, F.: Improving data quality in medical research: a monitoring architecture for clinical and translational data warehouses. In: 2020 IEEE 33rd International Symposium on Computer-Based Medical Systems (CBMS), pp. 415–420 (2020). IEEE

[58] Ayaz, M., Pasha, M.F., Alzahrani, M.Y., Budiarto, R., Stiawan, D.: The fast health interoperability resources (fhir) standard: systematic literature review of implementations, applications, challenges and opportunities. JMIR medical informatics **9**(7), 21929 (2021)

[59] Vorisek, C.N., Lehne, M., Klopfenstein, S.A.I., Mayer, P.J., Bartschke, A., Haese, T., Thun, S.: Fast healthcare interoperability resources (fhir) for interoperability in health research: systematic review. JMIR medical informatics **10**(7), 35724 (2022)

[60] Duda, S.N., Kennedy, N., Conway, D., Cheng, A.C., Nguyen, V., Zayas-Cabán, T., Harris, P.A.: Hl7 fhir-based tools and initiatives to support clinical research: a scoping review. Journal of the American Medical Informatics Association **29**(9), 1642–1653 (2022)

[61] Lehne, M., Luijten, S., Imbusch, P.V.F., Thun, S.: The use of fhir in digital health-a review of the scientific literature. GMDS **267**, 52–58 (2019)

[62] Schweitzer, M., Steger, B., Hoerbst, A., Augustin, M., Pfeifer, B., Hausmann, U., Baumgarten, D.: Data exchange standards in teleophthalmology: Current and future developments. In: dHealth 2022, pp. 270–277. IOS Press, ??? (2022)

[63] Torab-Miandoab, A., Samad-Soltani, T., Jodati, A., Rezaei-Hachesu, P.: Interoperability of heterogeneous health information systems: a systematic literature review. BMC Medical Informatics and Decision Making **23**(1), 18 (2023)

[64] Yogesh, M., Karthikeyan, J.: Health informatics: engaging modern healthcare units: a brief overview. Frontiers in Public Health **10**, 854688 (2022)

Table 5: limitations and challenges of FHIR-based data models

Categories	Summary of limitations / challenges
Data integration	requiring some manual ETL processes [14], reproducibility [24], maintaining robustness [14, 24], using only two datasets, information loss [15], challenging content normalization [16], single CRF with limited data elements, inadequate questions and data elements [25], manual download of FHIR resources [17], quality and completeness of the database documentation and non-automatic concept recognition, considerable data preparation process [18], using incomplete synthetic database [34], no data curation during transformation, bias in database [30], maintaining inadequate aspects of data [31], synchronization issues, hard coded mapping [26], privacy and confidentiality issues, limited corpora reuse [19], ignoring continuous changing of values over time [29], lack of comprehensive use of healthcare records due to lack of education and awareness [35], mapping rules were based on only two use cases, not including information about generic data [8], manual FHIR mapping, data of one setting was reviewed [40], the requirement to implement a structured information model to an existing data dictionary [41], issues with ADT dataset as a national reference (completeness/accuracy) [42]
Interoperability	reproducibility [24], organizational interoperability issues [28], privacy and confidentiality issues [19], synchronization issues, hard coded mapping [26], no evidence to attain a balance of functionality and portability, dissemination barriers due to development and integration cost [39]
Standardization	difficult rule-changing [14], semantic gaps between NLP system's data model and FHIR specification [16], more standardization needed [17], mapping accuracy issues [18], handling valid source system data with no match in FHIR [27], SNOMED-CT post-coordination limitations [28], not mapping to US Core as standard ontology, not mapping other databases linked to MIMIC-IV [30], not covering some clinical modifiers and qualifiers by FHIR redefinitions [19], SNOMED coverage restrictions [8], manual FHIR mapping [40], duplication of the mapping terms, a process was required to determine whether there is a need to define a new FHIR profile or continue with the existing profile [41], LOINC codes for some observations (SNOMED can be used instead), no available code systems for many value sets, lack of ubiquitous adoption of FHIR profiles due to the issues with SNOMED licence [42], requiring constant synchronization to the updates because the model is based on EBMonFHIR resources (have low maturity level and subject to changes), not all guideline information can be shown in FHIR resource format [43]
Performance	speed limitations due to transactional EHR [14], performance limitations [15], lack of sophisticated evaluation method [25], limited implementation assessment [34], performance validation issues*, no validation for real questions [32], technical challenges [33], model's limited functionality and lack of comprehensive specification [8], no evidence to attain a balance of functionality and portability [39], reduced response rate due to using online questionnaire [40], no execution engine available for representation format [43], Evaluation and validation [38]
Scalability / Generalizability	few resources were used [18], limited corpora reuse [19], further compatibility and generalizability experiments are needed [18], not using a real environment [31], possible bias when conducting a similar study, challenging generalizability for other cancers [32], restriction in the adaptability of best performing prediction model [29], covering diversity and using more complex methods to empower prediction is needed [29], the generalizability of the platform [36], no broad adoption of the app due to issues related to resources and expertise, best performs for specific programs [37]