Building the Semantic Interoperability Architecture Enabling Sustainable Post Market Safety Studies

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Motivation I

- We address the interoperability gap between clinical research and clinical care systems.
- Clinical trials are not adequate to ensure comprehensive drug safety
  - Limited size and scope
    - Not include patients with comorbid conditions and those being treated with concomitant medications
  - Designed to pick-up common problems not rare adverse events
  - Cannot detect long-term adverse events
Motivation II

- Post market safety studies address this problem, but
  - Reactive based on spontaneous case safety reports
    - Signal detection algorithms run by SRSs (such as WHO UMC) on top of these voluntarily sent reports
  - Medical professionals does not always see reporting a priority & detecting adverse events may not always be straightforward
    - It is estimated that medical practitioners report only about 5% of harmful drug side effects
  - Approximately 5% of all hospital admissions in Europe are due to an adverse drug reaction (ADR), and ADRs are the fifth most common cause of hospital deaths
    - An impact assessment carried out for the European Commission has estimated that ADRs cause 197,000 deaths per year in the EU, at a total cost of €79 billion
Objectives

- Enable effective integration and utilization of electronic health record (EHR) data to improve post-market safety activities on a proactive basis
  - EHR covers extended parts of the underlying medical histories, include more complete information on potential risk factors, and not restricted to patients who have experienced a suspected ADE
    - Denominator is missing in SRS data

- Aim to create the necessary infrastructure to enable secondary use of EHRs in an efficient and effective way for reinforcing the post market safety studies
How SALUS extends current spontaneous reporting system to seamlessly exploit the already existing clinical data at EHRs

An ideal system for ADR surveillance would combine the strengths of case reports with those of EHRs

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How SALUS enables exploratory/confirmatory signal detection and epidemiological research studies on top of heterogeneous EHRs

In order to realize nearly real time proactive post market safety studies, there needs to be a mechanism for screening the available heterogeneous and disparate EHRs for a specified time period for adverse event signal detection and also for conducting observational studies for validation of the suspected signals and for carrying out outcome research to see long term effects of drugs.

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Functional Interoperability

- SALUS will provide functional interoperability profiles to query EHRs for ADE identification, ADE reporting and signal follow-up studies and to subscribe clinical data for a selected cohort of patient for signal detection and outcome research over distributed EHRs.

- Examine syntactic and functional interoperability for re-use of EHRs for clinical trial execution like IHE RFD, CRD, DSC Profiles, HL7 Clinical Research Filtered Query Service Function Model (CRFQ SFM) and EHRCR functional profile.

- Propose the necessary extensions for enabling such a standard based interoperability architecture for post-market surveillance.
Semantic Interoperability Challenge

- Achieving Semantic interoperability to enable them to automatically interpret the queries and the resulting clinical data exchanged meaningfully and accurately in order to produce useful results
  - Identify a core set of common data elements (CDE) as meaningful EHR fragments that needs to be exchanged within the scope post market safety studies
    - Will be created according to the requirements of the selected SALUS use cases with high potential of enhancing patient safety. First of all content models will be developed for the selected use cases
  - Provide necessary tools to create, select, adapt and manage the CDEs in this core data set in conformance to ISO/IEC 11179 standard for metadata registries, and also for creating a semantic formal model of these CDEs as the common SALUS ontology
  - This evolving ontology will act as a common semantic dictionary of the clinical terms to be exchanged between EHR Systems and clinical research systems
    - Base our core data set on top of the existing standards including CDISC CDASH/ ODM, CDISC ASPIRE, BRIDG Domain model, available HL7 CDA templates and CEN EN 13606 archetypes for clinical care and we will extend them when necessary for the post market safety studies domain
  - Provide the tools to enable the clinical research systems to query the EHR systems through this semantic model
    - Do not expect every EHR System and clinical research system to be semantic aware to use the SALUS common ontology as their native clinical data representation formalism
    - Aim to enable them to communicate through their already existing domain information models such as CDISC ODM, HL7 CDA templates or CEN EN 13606 archetypes
    - Enable semantic mediation of the clinical data represented through syntactically different but semantically equivalent EHR content models to one another
  - In this way we aim to achieve semantic interoperability of meaningful fragments
Proposed Semantic Mediation Approach

An example case for iteratively evolving SALUS Harmonized ontology – Integrating Eligibility Criteria Content Models, database schemas of proprietary EHR resources.
Two complementary approaches will be followed:

- By providing a semantic interoperability layer on top of the functional interoperability profiles to be developed in WP5: clinical research and clinical care systems can communicate through using well accepted standards like HL7 CDA, CEN EN 13606 archetypes, and CDISC ODMs within the scope of well defined transactions, yet be able to meaningfully interpret these syntactically different but semantically similar content models.

- By enabling the development of semantic interfaces on top of the clinical information sources, so that clinical data exchange among clinical care and research systems can be handled based on a common semantic model.

- Provide a migration path from clinical care and research systems that can communicate through semantically enhanced functional interoperability profiles to clinical care and research systems that support full-fledged semantic systems enabling semantic interfaces through our harmonized patient safety ontology.
Proposed Semantic Mediation Approach

SALUS Functional and semantic interoperability layer cooperating for seamless communication of EHR and Clinical research Systems
Selected Use Cases

- Enabling Semi-automatic Notification of Suspected ADEs and Reporting ADEs within a Hospital
  - Enabling Notification of Suspected ADEs
  - Enabling Semi-automatic ADE Reporting

- Supporting Clinical Evaluation of a Potential Signal through Accessing the EHRs
  - Characterizing the cases and contrasting them to a background population
  - Temporal pattern characterization

- Running Exploratory Analysis Studies over EHRs for Signal Detection
  - Manual clinical review of relevant medical history

- Using EHRs as secondary use data sources for Post Marketing safety studies
  - Estimate incidence rates of CHF in diabetic patients with a recent acute coronary syndrome (ACS) event on different diabetic medications
Step 1. EHR extracts pre-population data as CCD

Step 2. Pre-population data in CCD is mapped to BRIDG OWL representation

Step 3. An EDC processes a study design model to extract the CDASH terms annotating the data fields in the CRF

Step 4. Data Fields in CRF are queried from the Pre-population data using the SPARQL mappings of CDASH variables

Step 5. The CRF is pre-populated and presented to the EHR system to be further checked and completed by the health care professional

Step 6. Filled CRF is sent

Step 7. Patient Medical history can be queried through CDASH/SDTM variables and terminology systems codes to collect other underlying conditions and active medications of the patient

Statistical Analysis Tool (Regulatory Body)
Initial Prototype

Harmonizing with Content Standards

- Standard Schema definition (e.g. HL7 CDA XML, semantic model of Schema/HL7 Study Design RMIM, or HL7 SDM RMIM RDF)
- Mapping Def (SPIN rules)

Importing Clinical Documents to Semantic Framework

- Clinical content (e.g. patient summary in HL7 CCD, or a HL7 Study Design Message)
- RDF representation of clinical content (e.g. HL7 CDA instance or HL7 SDM instance)
- Rule to link with terminology ontologies

Exporting Clinical Documents from the Semantic Framework

- Clinical content (CDISC Study Design Document)
- RDF representation of clinical contents (e.g. CDISC SDM instance)

BioPortal Repository

- Rule to add OID
- SNOMEDCT RDF and its mappings

Importing Biomedical Ontologies and Mappings

- SPARQL queries for CDISC SDTM Variables
- SPARQL queries for CDISC CDASH Variables
- SPARQL queries for HL7 CRFQ Variables

SPARQL Library for Data Set Standards

- SPARQL queries for HL7 CRFQ Variables

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Conclusion

- **End results:**
  - The necessary functional and semantic interoperability infrastructure to enable secondary use of EHR data in an efficient and effective way for reinforcing the post market safety studies.
  - Considering several different initiatives and standards to be harmonized consistently
  - A ISO/IEC 11179 compliant CDE Repository
    - A common ontology based on the selected CDEs
    - BRIDG, HL7 Clinical Statement Model, CCD, EN 13606 based templates, CDISC Share
  - ADE Notification & Reporting Tool
  - Temporal Pattern Characterization Tool
  - Signal Detection over EHRs
    - Collaboration with OMOP Project: SALUS will make the query results available in OMOP CDM format
  - Security & Privacy Architecture
    - De-identification (Pseudonymization) algorithms, Audit mechanisms, Node authentication, TLS
Thank you, Questions?

http://www.salusproject.eu

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