

“OPeN” - The National Adverse Reactions Database in the Croatian eHealth System

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Abstract— The Croatian Agency for Medicinal Products and Medical Devices is currently implementing the OPeN project. Once complete, the project will automate the acquisition of pharmacovigilance data from various clinical Information Technology (IT) systems and provide data syndication in the Croatian National Adverse Reactions Database. It will provide a significant contribution to the public health system in Croatia. This paper presents the workings of the OPeN project in the context of the Croatian eHealth system.

Keywords— *adverse drug reactions; eHealth system; National Adverse Reactions Database; OPeN; pharmacovigilance.*

I. INTRODUCTION

The paper “OPeN: Linking the National Adverse Reactions Database with Clinical IT Systems in Croatia,” presented at the Tenth International Conference on eHealth, Telemedicine, and Social Medicine (eTELEMED) in March 2018 in Rome, describes the OPeN system, its mechanisms and expected benefits for the public health system in Croatia [1]. (Figures 2, 3 and 5 in this article were presented for the first time in our eTELEMED conference paper.) “OPeN” is a shortened form of the phrase “online platform for adverse drug reactions (ADRs) electronic reporting” (Online Platforma za elektroničku prijavu Nuspojava, in the Croatian language). The same authors will present an extended version of the subject matter, further addressing implementation of the OPeN project throughout the entire Croatian eHealth system. It is also an update of the work presented at the eTELEMED conference given that OPeN has already been set up on a production environment.

The direct beneficiary of the project is the Croatian Agency for Medicinal Products and Medical Devices (HALMED) [2] and is the national competent authority (NCA) in charge of regulating medicinal products and medical devices in the country. HALMED conducts drug-related pre-approval and post-approval processes; the later comprising pharmacovigilance activities for the detection, analysis, evaluation, interpretation, and deterrence of noxious and unintended drug reactions (i.e., ADRs) [3] [4].

Pharmacovigilance (PhV) is a data-driven discipline where analysis of ADRs relies on multiple data sources such as spontaneous reporting [5], data mining [6] [7], as well as the direct reporting from healthcare professionals (HCPs) working in clinical IT systems. Although spontaneous reporting is a valuable pharmacovigilance source [5], a noticeable problem of underreporting exists [8]. Hence, the European [9]–[11] and global community has standardised

pharmacovigilance practices by issuing general guides [12] and data-related specifications [13] [14], as well as introducing standards for the field [15]–[17]. Therefore, the latter two data-gathering techniques and related data sources are advancements in pharmacovigilance over the last decade. Data mining, as well as direct relevant [18] input from HCPs working in clinical IT systems, have mitigated the issue of underreporting [19]. The contribution by HCPs also increases the data quality because the data is interpreted correctly and communicated by professionals.

This paper systematises and expands the work presented at the eTELEMED conference which described the development of the OPeN system and points out the specific circumstances and its broader ecosystem. OPeN is a system based on the Croatian National Adverse Reactions Database which is maintained by HALMED. Since the interoperability of eHealth components is a significant aspect of “efficiency in the healthcare sector” [20], OPeN aims to achieve integration with the Croatian eHealth environment. The environment, specifically the Croatian Central Health Information System (CEZIH), consists of: the Healthcare Networking Information System (HNIS) operating as an exchange platform, Electronic Healthcare Record (EHR), patient register, register of HCPs, messaging subsystem based on Health Level Seven International (HL7v3 and HL7v2) messages, online patient healthcare website, implemented through the eCitizen website, and specialised services related to e-prescriptions, e-laboratory referrals, e-booking hospital admittance, and numerous other functions [21]. CEZIH was established in 2002 [22]. It started as a primary healthcare IT system, but underwent continual expansion – and in 2010 included the ePrescription service, and later in 2016 incorporated EHR and the patient healthcare website or portal [22]. It operates using other additional client applications for paediatric healthcare, gynaecology, dental healthcare, laboratory diagnostics, pharmacies, hospital and clinical IT systems. The Croatian Health Insurance Fund is responsible for maintaining CEZIH.

In Section II of this article, we will briefly touch upon European projects that have led to the development of the OPeN project and will subsequently describe its goal and main phases. Section III describes the system modules, technical characteristics and mechanisms, and use by internal HALMED users and external HCPs. Further on, Section IV discusses efforts to increase the number and quality of ADRs in Croatia, as well as direct reporting as advancement in Croatian pharmacovigilance, and briefly compares pharmacovigilance systems with direct reporting capabilities.

We will discuss why and how specific pharmacovigilance mechanisms were included in other European systems led by other NCAs and we will compare them to OPeN and efforts taken by HALMED in recent years. Examples from similar European systems were studied as they use direct ADR reporting sourced from clinical systems, which was the primary mechanism for achieving the OPeN project. Finally, in the same section, we discuss the Croatian eHealth environment and the role of OPeN. Section V provides a conclusion, while Section VI outlines future work on the project as well as feasible and desirable advancements in the entire ecosystem.

II. HALMED'S PARTICIPATION IN IT PROJECTS IN PHARMACOVIGILANCE AND THE LIFECYCLE OF THE OPeN PROJECT

HALMED is responsible for maintaining the national ADR database called VigiBase which is provided by the Uppsala Monitoring Centre (UMC) and the World Health Organization (WHO). To increase capacity in acquiring ADR data from multiple sources, HALMED has participated in two respected and well connected European IT projects in pharmacovigilance– European Commission (EC) Joint Action SCOPE (Strengthening Collaboration for Operating Pharmacovigilance), and Recognising Adverse Drug Reactions (WEB-RADR). SCOPE is a joint action project at the EU level focusing on developing ADR reporting mechanisms [23]. It has produced recommendations for facilitating data collection, data syndication and data disposal to other systems for further processing. WEB-RADR was started in late 2014 and deals with mobile technology, data mining and social media in pharmacovigilance. The project was financed by an initiative that included the 7th Framework Programme means and private contribution, so it represented a private-public partnership between the EU and the European Federation of Pharmaceutical Industries and Associations (EFPIA). Croatian (HALMED), the Dutch MEB (Medicines Evaluation Board), and British MHRA (Medicines and Healthcare Products Regulatory Agency) were NCAs that developed mobile apps for reporting ADRs under WEB-RADR in 2015 and 2016 [24] (see Figure 1). Generally speaking, the projects were well supported by pharmacovigilance practitioners and HCPs in Europe.



Figure 1: HALMED's mobile app QR code for ADR reporting

HALMED has gained experience from these international projects and subsequently initiated a new project called OPeN. [25] OPeN conforms entirely to the SCOPE project recommendation for NCAs who should “integrate suspected ADR reporting into clinical IT systems” [26]. The goal of the OPeN project is to increase both the

number and quality of ADR reports and facilitate communication between HCPs and NCAs through connected clinical IT systems and national ADR databases. The project includes some risks, as all compound projects usually do. Establishing a system as complex as OPeN involves many different institutions and stakeholders (Croatian Ministry of Health, Croatian Health Insurance Fund, Croatian National Institute of Public Health, and IT companies providing solutions and services to the healthcare industry). The most significant risks in this entire process were and still are ensuring necessary funding and providing timely coordination of activities between various stakeholders. The initial plan was to connect OPeN to CEZIH [27] and different hospital IT systems. However, this has not yet been done, with the HALMED staff actively working on it. A possible risk in implementing such integration is the fact that the maintaining of CEZIH is not HALMED's responsibility. Another risk is that there are five clinical hospital centres, three clinical hospitals, five clinics, 20 general hospitals and 24 specialized hospitals in Croatia [28], as well as other participating institutions. Each has various levels of computerisation, and HCPs in these various hospitals use different IT solutions. HALMED has developed the OPeN system to a level where it is now functionally ready; however, other main Croatian stakeholders are required to incorporate the system into the national healthcare ecosystem. The ideal path that should be taken is to enforce providers to incorporate ADR reporting elements into their clinical software products, with various approaches for solving communication issues between systems.

Regarding the project lifecycle, HALMED has finished the first phase of system development, and the project is entering the second phase (see Figure 2). The first phase dealt with facilitating HALMED's internal ADR processing and development of web reporting forms, smart PDF forms and web services to be integrated into the respective clinical IT systems. The result of the first phase is a functional web-based ADR reporting form and completed OPeN ingest functionality. The OPeN system interface is user-friendly to simplify data entry and decrease the time required for data entry. During ADR reporting, an individual HCP selects field values from various lists of medicinal products, institutions, units, and measurements. Users can also choose from one of the existing templates for new reports. Although the web-based application OPeN is fully functional and it can be used for data transmission, HALMED is aiming to sign the protocol with the Croatian National Institute of Public Health. This protocol is essential for data exchange between the institute and HALMED and the future use of OPeN in the entire Croatian eHealth ecosystem. This is the goal of the second phase. The OPeN system will be fully operational nationally only after strengthening such cooperation. This procedure turned out to be a complicated legal and administrative matter in Croatia, but the institute has received permission from the Croatian Personal Data Protection Agency to share the data, acting as the national data-protection authority. Moreover,

the Croatian Ministry of Health has adopted certain activities for OPeN as one of their strategic goals for 2019. HALMED has also declared OPeN as one of its general goals in its official 2019-2021 Strategic Plan. In parallel with the signing of the data protocol and preparation of the second phase, HALMED has begun planning the third phase (see Figure 2), i.e., upgrading the system with an additional module that informs HCPs and facilitates their ongoing training in the form of online courses.

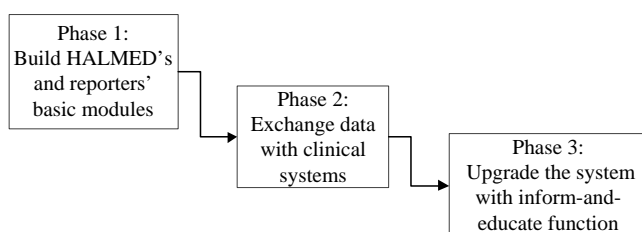


Figure 2. Development phases for the OPeN system.

III. OPEN – DEVELOPMENT, MECHANISMS AND RESULTS

HALMED's goal in this project is to automate direct reporting of adverse drug reactions by HCPs, using existing workplace IT systems.

OPeN has been developed as a web-based application that consists of a database, a web interface, and web services for integration with other IT systems (external clinical IT systems and other IT systems at HALMED). OPeN is based on Windows technology and developed using the .NET Framework, whereas the data is stored in the as Microsoft's Structured Query Language on a server database (MS SQL). The database is organized in multiple schemes and contains data and procedures for system operation, such as configuration data, user data, data on healthcare facilities, and all data on adverse drug reactions including their logging and processing. Wherever possible, the data is structured into more than 40 data lists, a part of which is accessible to users via a web service.

A firewall and the Secure Sockets Layer (SSL) protocol protects the entire system. Access and data protection are established through domain admin policies for internal users (Windows Active Directory) and for external users. Backup procedures are performed regularly.

The scenario is as follows: an individual HCP submits a report and transfer it to HALMED, where assigned staff processes the report (see Figure 3).

There are three possible ways of sending data on side effects to OPeN; via the Internet and web application, sending the prefilled smart PDF document via e-mail or directly via the IT systems HCPs use at their workplace (if the system is connected to OPeN, as predicted by the phase 2 result).

The web layer of OPeN consists of two modules: a module for HALMED employees and a module for external

users (HCPs). HALMED employees use the system to register and validate received reports, detect duplicates, assign them to assessors, and track further processing and steps, such as forwarding them to the EudraVigilance system [29], as well as other tasks. The module for HALMED employees is also connected to the HALMED Enterprise Content Management System (ECMS) via web services, where all the digital records are stored. These digital records are available for reading and editing in the OPeN system throughout the entire process.

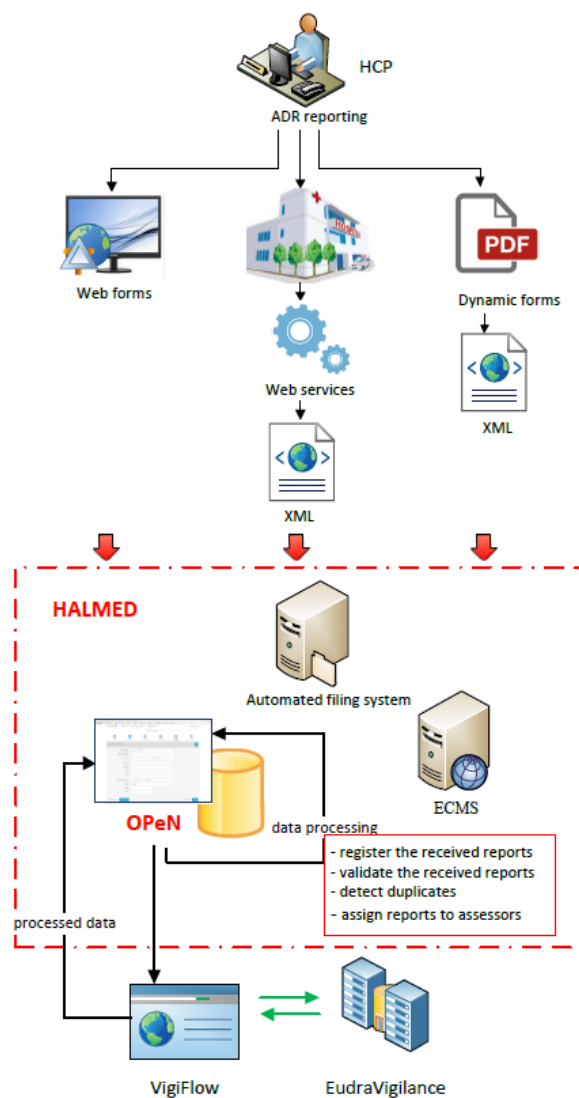


Figure 3. The OPeN workflow

Registered HCPs use the module assigned for external users to report adverse drug reactions. In the form for entering the drug or vaccine data, users enter one or more drugs (one or more vaccines which are suspected) or concomitant substances (see Figure 4). The fields in Figure 4 are as follows: Drug (medicinal product), Active

Ingredient, Marketing Authorisation Holder (MAH), Dosage, the checkbox for Vaccines, the checkbox for Suspected drug, Drug Consumption Start Date, Drug Consumption End Date, its Duration, Batch Number for the drug, and Single Dosage. The drugs are selected from the list and then other drug data, such as the active substance, dosage and MAH, are completed automatically. The user can also specify the name of the drug.

Figure 4. Form for entering one or more suspected drugs

OPeN users can enter optional information for any drug such as start date of drug consumption, end date of drug consumption, duration of treatment, dose interval, amount of administered doses in a selected interval, single dosage, batch number, indication, and administration route. Also, users can enter information about whether adverse reactions ceased after completing therapy or whether adverse reactions reappeared upon re-administering the drug. In the application dashboard, the reporter can view all entered adverse drug reactions and a status report. Views include an overview of unrecorded side effects, received side effects, side effects awaiting acceptance, side effects assigned to somebody, side effects approaching the processing deadline, side effects awaiting a severity rating, side effects assigned

to the current user, side effects awaiting entry, as well as side effects assigned to the current user and awaiting a severity rating. The system alerts the user if data concerning an applicant or patient is missing, or if an error has occurred such as an upload error or check-in error, and it shows the status of the application. Figure 5 shows the OPeN interface; with the example indicating creation dates and statuses “Received in OPeN” and “Task accepted” in the last row.

Kreirano	Status
19.7.2017.	Zaprimljeno u OPeN
19.7.2017.	Zaprimljeno u OPeN
19.7.2017.	Zaprimljeno u OPeN
19.7.2017.	Prihvaćeno zaduženje
20.7.2017.	Čeka prihvrat zaduženj
19.7.2017.	Završeno
19.7.2017.	Poslan XML
19.7.2017.	Završeno

Figure 5. The OPeN interface for data entry

All institutions that participate in data exchange use the same list of HCP authentication data. This facilitates exchanging data without additional authentication when sending the data to HALMED. A common list provides data traceability. Data exchanged between internal and external systems is in XML data format, and XML structures adhere to E2B-R2 and E2B-R3 formats [13] [14]. ADR reporting is carried out via an HTTP POST request to the endpoint: <http://open.halmed.hr/client/#/login>. All required lists can be downloaded via the web service available on the following website:

<http://open.halmed.hr/CodeBookService/CodeBookService.svc>. The site provides the following lists: Doubt, Consequence, Age Unit, Gender, Medication, Outcome, Duration Unit, Time from Consumption to Reaction Unit, Side Effect Medicine Correlation, Measurement Unit, Dosing Interval Unit, Application Type, Drug Consumption Change, Drug Reapplication Status, Drug Discontinuation, Application Location, Profession, Vocation, County, and Country.

In the first phase of the project, HALMED also developed a smart PDF form containing embedded lists. The form is available on the HALMED and OPeN websites

[25]. Anyone can access the form, complete it and send it via e-mail. OPeN automatically loads data from the form into the OPeN database, eliminating the need to enter data manually. HALMED has provided instructions on various reporting tasks for the general public, patients and HCPs on the PhV section of its website (<http://www.halmed.hr/en/Farmakovigilancija/Kako-prijaviti-nuspojavu/> for English page).

IV. DISCUSSION ON THE OPeN AND EHEALTH SYSTEMS IN CROATIA

Due to their significant contribution to an efficient eHealth ecosystem, we will highlight some of the OPeN possibilities, such as integration and communication with other systems, as well as current coding and data mapping abilities. To grasp the importance of direct reporting and main points of the OPeN system, we will provide a historical development of reporting in Croatia, benefits of the reporting function, direct reporting trends in other countries, and the national eHealth system as a broader field in the direct reporting.

A. Efforts to increase the number and quality of ADRs in Croatia over the last decade

Spontaneous ADR reporting is the keystone of pharmacovigilance. A sufficient number of high-quality ADR reports are directly correlated to the effectiveness of ADR system capacity in detecting drug safety issues. ADR systems rely on the goodwill of HCPs and patients, not only on identifying suspected ADR reports but also reporting them. ADR reporting schemes are recognised as being underreported [8] [30] [31]. Directive 2010/84/EU, which came into force in 2013, identified this issue and stated that NCAs need to encourage and improve reporting of ADRs. According to Article 102 of the Directive, NCAs shall “take all appropriate measures to encourage patients, doctors, pharmacists and other healthcare professionals to report suspected adverse reactions to the national competent authority” [32]. Heads of medicines agencies (HMA) incorporated the aim of the Directive into their 2011-2015 Strategy [33]. HMA aims to support the strengthening of spontaneous ADR reporting systems, indicating four main complementary approaches as a means of improving ADR reporting and achieving a more robust national pharmacovigilance system: (1) education, (2) motivation, (3) promotion, and (4) facilitation of ADR reporting, all of which are mainly directed to HCPs and patients.

Throughout the last decade, HALMED has joined in numerous activities to increase the number and quality of reported ADRs in Croatia. The number of spontaneous ADR reports increased from 856 in 2007 to 3486 in 2016, ranking Croatia in the top ten countries in the world for a number of ADRs per million inhabitants [34]. Education, motivation, and promotion have been extensively used and combined with different ways of making reporting easier. This was done by introducing novel methods for capturing

ADRs: an online reporting form for patients to complete as well as a mobile app for patients and HCPs. The online reporting form was launched in 2012, and by 2016 a total of 20% of all ADRs were received through this channel. Although HALMED intended the online reporting form to be for patients, it was also widely used by HCPs. The PhV mobile app was introduced in 2016 (through the project WEB-RADR) and accounted for the 2% of ADR received in 2016. The focus was on activities aimed at making reporting easier. HALMED started introducing electronic reporting which encouraged rationalisation of internal ADR processing. The main reasoning behind this was to decrease manual entries into the national ADR database. This issue has gained in importance as an increasing number of received ADRs begins to have a real impact on resources available to other pharmacovigilance processes at HALMED (e.g., assessments of risk management plans, periodic update of safety reports).

B. Direct reporting from clinical systems - an advancement in pharmacovigilance

Although the regulatory workload at HALMED has increased substantially since 2013, there remains an active commitment to improving the national PhV system, as well as opening up possibilities for detecting signals and safety issues. This was the reason for planning and starting the OPeN project. OPeN aims to automate the internal handling of reported ADRs and to further increase both the number and quality of ADR reports transmitted to HALMED. Capturing ADR reports from online reporting forms and clinical systems should ensure this. The idea behind OPeN is to build a system that will allow communication between clinical IT systems and the national ADR database. HALMED considers the capturing of ADR reports from clinical systems in electronic form to be the most challenging part of the project. Direct reporting from clinical systems, however, has many advantages. It improves the efficacy of reporting of HCPs by making the completion of forms easier as it uses data from patient records and automates data entry methods. HALMED considers it to be a way of promoting ADR reporting in general. Based on a systematic review and meta-analysis published by I. Ribeiro-Vaz et al. [35], projects that aim to promote ADR reporting by harnessing IT solutions are an increasing trend. According to their aggregate analysis, these solutions have doubled the number of captured ADR reports.

Reporting from the clinical system helps in acquiring comprehensive information on ADRs. It facilitates case assessment by providing the surrounding circumstances for ADRs. An added value is the ability to prompt reporters to complete a report in the system once specific tasks are completed, e.g., withdrawing a drug from administered therapy. It can also prompt a reporter to enter more specific report data (e.g., the batch number if ADR comes from vaccines and biologicals). This ADR information is rarely

captured in paper form; however, it can be crucial in understanding ADR causes.

An additional benefit of an automatic data entry method in direct ADR reporting from a clinical system is the use of controlled data entries. Where applicable, ADR reporters may use data registries (e.g., medicinal product registry) to facilitate the data entry method. Another benefit of using IT solutions is using data validation rules and making it easier to receive accurate and valid reports. Consequently, national ADR databases are becoming more accurate. It reduces the need to contact a reporter in case of non-valid ADRs. Rules of reporting should meet the applicable ICH E2B standards [13] [14], and minimum required data. Additional validation rules should also be incorporated to meet business or regulatory requirements. Also, the use of dictionaries, including the mapping of dictionaries, helps establish standardised terminology and coding terms for assessors. The use of dictionaries represents a significant benefit for any pharmacovigilance system. The second phase of OPeN addresses these very issues.

C. A brief comparison of pharmacovigilance systems with mechanisms for capturing ADRs from clinical systems

According to the SCOPE results, there are only 3 NCAs or regulatory agencies that utilize the possibility of capturing ADRs from clinical systems: the Spanish AEMPS (Agencia Española de Medicamentos y Productos Sanitarios), the British MHRA (Medicines and Healthcare products Regulatory Agency) and the Netherlands Pharmacovigilance Centre Lareb [36] - [38]. Their systems mainly aim to retrieve ADRs from general practitioners (GPs). This is a logical decision given that GPs have access to most of a patient's health information.

Although systems differ, their experiences indicate that the integration of ADR reporting into electronic health records, primary healthcare, and e-prescription systems correlates positively with an increased number of received ADR reports and quality of received information. Spain integrated its ADR reporting system with HER, the primary healthcare and e-prescription solution back in 2010. The Spanish use a 'Nomenclator' dictionary maintained by AEMPS. The use of the International Classification of Diseases (ICD) is also recommended.

In the UK, for example, during the pilot phase of the system in 2011, automatic ADR reporting feature was added to a primary care system (SystemOne) for GPs. Analysis of received Yellow Cards showed an increase for GP ADR reports of almost 50% compared to 2010. Specific information, the standard for electronic Yellow Card reporting, was developed for the English National Health Service (NHS) in 2012 [39]. It was based on the ICH E2B(R2) standard [13] and prescribed use of the electronic Yellow Card message.

In the Netherlands, professional bodies and GPs have implemented an electronic reporting module linked to the GPs medical records. The Netherlands PhV Centre Lareb

integrated the reporting of suspected ADRs in healthcare systems using a specific method. Once a physician enters an ADR in patient records, an alert pops up to prompt reporting of ADRs. It opens a partly completed reporting form on the GP's computer screen for further completion. The second method is to send reported ADRs which are recorded in registries automatically to Lareb. The initiative commenced in 2014, and the first reports from the registry began arriving in December 2015. Both initiatives were in the pilot phase during the SCOPE report, with a few sites sending the reports. From mid-March 2016, plans focused on developing reporting forms for the GP information system. With regards to education, there has been no special education for reporting ADRs using these two new methods. The UK and Spanish systems follow a similar concept. There are some differences between the systems. ADRs received from clinical systems in Spain are not automatically uploaded into the national database at Farmacovigilancia Española, Datos de Reacciones Adversas (FEDRA), but pass through regional PhV centers. Also, the ADR description is authored by the HCP, while the UK system codes the ADRs in compliance with the dictionary called the *Systematized Nomenclature of Medicine* (SNOMED) [40]. The MHRA has implemented a mapping between the SNOMED terms and the *Medical Dictionary for Regulatory Activities* (MedDRA) [41] which is standard terminology used for coding ADRs worldwide. It enables ADR reports to be automatically loaded into the PhV database at MHRA without coding ADRs.

In comparison, OPeN allows direct upload of ADR reports to the national database. However, coding of ADRs by the reporter will not be possible. Also, the Croatian eHealth system does not use SNOMED, but coding lists are agreed upon at a national level to ensure interoperability [20]. HCPs in Croatia use the International Statistical Classification of Diseases and Related Health Problems 10 (ICD 10) terminology for coding medical terms [42], and there is no mapping to MedDRA.

Also, OPeN provides two-way communication with reporters, mainly for retrieving follow-up information. We believe this is the benefit our system offers, although details on the communication possibilities within the UK or Spanish systems are not widely available. There is limited published information on particular data elements of both systems. We were able to compare our systems solely by actively participating in the SCOPE project. However, information on the systems may be outdated, given that SCOPE includes data only before 2013. Moreover, it is a challenge in finding information about publication activities from other countries when implementing ADR reporting from clinical systems. Previous research of the systems outlined above has enabled the HALMED team to avoid some problems in developing, implementing, and fine-tuning of the OPeN system. The primary challenge in this type of projects in other countries was the integration of the reporting form into the particular system logically and

without seeking too much or too little additional information. Ensuring patient privacy was also important. HALMED's team members have used these valuable lessons during the development of the OPeN system.

D. OPeN - vital to the Croatian eHealth ecosystem

In general, eHealth systems consist of electronic medical records (EMR) produced by particular HCPs, EHR (generated by all HCPs), as well as personal healthcare records (PHR) verified by patients [20].

The eHealth system in Croatia provides two functions: an integration platform for local information systems used in GP practices, pharmacies, laboratories, hospitals, and a centralised national application accessible via a web interface. Generally, the business process runs in the following manner: nurses and GPs use client applications for processing patient information. Client applications utilize captured information, transforming it into patient summaries, prescriptions, referrals for hospitalization or specialist reports, referrals to laboratory analyses, and the like. These messages are sent to the central core of CEZIH which is available to other healthcare participants. For example, a pharmacist retrieves a prescription from his client-side application, dispenses the particular medication and sends the relevant information back to the CEZIH centre, which is also accessible to the prescriber. An Analogous process exists with referrals and which are retrieved by hospital or laboratory personnel, after which the discharge letters and laboratory results are sent back to CEZIH, and subsequently to the referring party [22]. Additional available services are infectious disease reporting, malignant disease reporting, sick leave reports, adverse effects during immunization, retrieval of administrative information from insurance perspectives and other types of reports. Authentication is supported with smart cards for HCPs, and information security is supported with CEZIH and client applications such as VPN, firewall, SSL/TLS and encryption. [22]. Messages are stored by the system and have a non-repudiation quality [22]. Some of the most relevant information that originates from mechanisms such as patient visit summaries, ePrescription and eReferral are transformed and provided to healthcare professionals via the EHR application after establishing appropriate authorization and in line with patient consent. The limited scope of medical information is also available for review via dedicated patient websites where consent for accessing EHR can also be given and revoked, and information on access to a patient's EHR can be reviewed.

The design enables OPeN to anticipate connections between the actual system and the Croatian eHealth environment (CEZIH) as well as related physician, pharmacy and hospital IT systems. Most of the data required for reporting ADRs is already contained in the IT systems of HCPs, hence filling out the forms takes less time, and it also simplifies the process of sending data to HALMED. The outcome is an increase in the quality of transmitted data,

less chance of errors during data entry and preventing the submission of incorrect or incomplete forms.

V. CONCLUSIONS AND EXPECTED BENEFITS

Submissions of timely and properly completed ADR reports increases the data available to NCAs and their capacity to raise public health. It improves the ability NCAs to detect, identify, investigate and act on potential drug safety issues.

Pharmacovigilance professionals consider the integration of clinical IT systems and ADR databases as a bleeding edge tool for increasing both the number and quality of captured ADRs. HALMED has established OPeN for this very reason. As the Croatian NCA for drugs, HALMED has started an initiative that has aimed to integrate the national ADR database, CEZIH, and various hospitals IT systems. The expected benefits include:

- Facilitation and promotion of ADR reporting,
- A higher number and better quality of reports,
- Less manual data entry and data processing time per the report,
- Standardisation, clarification of professional terms, dictionaries,
- The introduction of analytics, advancement in tracking key performance indicators (KPI) and signals, planning for BI features,
- Improving guidance on drug prescriptions,
- Sophisticated and proactive protection of public healthcare based on interpretation of complex drug reaction reports provided by modern IT solutions.

The last benefit stems from the result of integrating OPeN and CEZIH, and this will be possible once data between the Croatian Health Insurance Fund and HALMED, or their CEZIH and OPeN systems is exchanged.

VI. FURTHER WORK

An efficient and connected healthcare system facilitates the protection of patients, efforts by HCPs and has benefits for all other stakeholders in the national healthcare industry. The OPeN system is an excellent example of utilizing important pharmacovigilance mechanisms and convenient technological elements in the national health system. HALMED will upgrade it with additional functions in the future, and we firmly believe that the sustainability of the project is ensured.

REFERENCES

- [1] A. Rajh, D. Sudic, and K. Gvozdanovic, "OPeN: Linking the National Adverse Reactions Database with Clinical IT Systems in Croatia." *The Tenth International Conference on eHealth, Telemedicine, and Social Medicine (eTELEMED) IARIA*, March 2018, pp. 54-59.
- [2] Agency for Medicinal Products and Medical Devices of Croatia. *About HALMED*. [Online], Available from: <http://www.halmed.hr/en/O-HALMED-u/> [last access: 11/08/2018]
- [3] European Medicines Agency. *Pharmacovigilance*. [Online], Available from:

- http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000258.jsp [last access: 11/08/2018]
- [4] I. R. Edwards and J. K. Aronson, "Adverse drug reactions: definitions, diagnosis, and management," *The Lancet*, vol. 356, issue 9237, pp. 1255 – 1259, Oct. 2000.
 - [5] N. Mirosevic Skvrce et al., "Adverse drug reactions caused by drug-drug interactions reported to Croatian Agency for Medicinal Products and Medical Devices: a retrospective observational study," *Clinical Sciences*, vol. 52, issue. 5, pp. 604-614, Oct. 2011, doi: 10.3325/cmj.2011.52.604
 - [6] M. Liu, M.E. Matheny, Y. Hu, and H. Xu, "Data Mining Methodologies for Pharmacovigilance," *ACM SIGKDD Explorations Newsletter*, vol. 14, issue 1, pp. 35-42, June 2012, doi: 10.1145/2408736.2408742
 - [7] A. M. Wilson, L. Thabane, and A. Holbrook, "Application of data mining techniques in pharmacovigilance," *British Journal of Clinical Pharmacology*, vol. 57, issue 2, pp. 127–134, Feb. 2004, doi:10.1046/j.1365-2125.2003.01968.x
 - [8] L. Hazell and S.A. Shakir, "Under-reporting of adverse drug reactions: a systematic review," *Drug Saf.* 2006; vol. 29, issue. 5, pp. 385-396, May 2006, doi:10.2165/00002018-200629050-00003
 - [9] European Medicines Agency. Information Management Division. *Master Data Management Roadmap: Substance, Product, Organisation and Referential data*, 23 April 2015. [Online]. Available from: http://www.ema.europa.eu/ema/pages/includes/document/open_document.jsp?webContentId=WC500186290 [last access: 11/08/2018]
 - [10] European Medicines Agency. *Monitoring of medical literature and entry of adverse reaction reports into EudraVigilance*. [Online]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000633.jsp&mid=WC0b01ac05808ce84c [last access: 11/08/2018]
 - [11] European Medicines Agency. *Reporting requirements for marketing-authorisation holder*. [Online]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000594.jsp& [last access: 11/08/2018]
 - [12] ICH, FDA, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER). *Guidance for Industry - E2B(R3) Electronic Transmission of Individual Case Safety Reports (ICSRs) Implementation Guide – Data Elements and Message Specification*, February 2014.
 - [13] ICH E2B(R2). *Individual Case Safety Report (ICSR) Specification and Related Files*. [Online]. Available from: <http://www.ich.org/products/electronic-standards.html> [last access: 08/08/2018]
 - [14] ICH E2B(R3). *Individual Case Safety Report (ICSR) Specification and Related Files*. Available from: <http://www.ich.org/products/electronic-standards.html> [last access: 08/08/2018]
 - [15] European Medicines Agency. *Substance, Product, Organisation and Referential (SPOR) master data*. [Online]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000645.jsp&mid=WC0b01ac058078fbe2 [last access: 11/08/2018]
 - [16] ISO/HL7 27953-1: 2011 Health informatics – Individual Case Safety Reports (ICSRs) in pharmacovigilance – Part 1: The framework for adverse event reporting
 - [17] ISO/HL7 27953-2: 2011 Health informatics – Individual Case Safety Reports (ICSRs) in pharmacovigilance – Part 2: Human pharmaceutical reporting requirements for ICSR
 - [18] T. Saracevic, "Relevance: A Review of and a Framework for Thinking on the Notion in Information Science," *Journal of American Society for Information Science*, vol.26, issue 6, pp. 321-343, Nov. 1975, doi: 10.1002/asi.4630260604
 - [19] J. Almenoff et al., "Perspectives on the Use of Data Mining in Pharmacovigilance," *Drug-Safety* vol 28 (11), pp. 981-1007, 2005, doi:10.2165/00002018-200528110-00002
 - [20] D. Gvozdanovic et al. (2015), "Interoperability Within E-Health Arena." In *Proceedings of the Fourth International Conference on Telecommunications and Remote Sensing* (Vol. 1, ICTRS, pp. 81-86). Bulgaria: SCITEPRESS. doi:10.5220/0005889800810086
 - [21] 2016 Annual Report Ericsson Nikola Tesla Group General Report. (2016). Retrieved from https://www.ericsson.hr/documents/20181/21890/ar2016_en_general.pdf/495d6bff-e782-4878-ba8a-6cfc9603f082 August, 2018.
 - [22] Ministry of Health of the Republic of Croatia. (2013, November 26). Centralni zdravstveni informacijski sustav Republike Hrvatske (CEZIH) - Koncept sustava (2/15517-FCPBA 101 24/8 Uhr Rev B). Retrieved August, 2018, from http://www.cezih.hr/pzz/dokumentacija/01_00_CEZIH_koncept_sustava.pdf
 - [23] SCOPE Work Package 4 ADR Collection, *IT Systems for ADR Reporting: Best Practice Guide* [Online], Available from: http://www.scopejointaction.eu/_assets/files/WP4-IT-Systems-for-ADR-Reporting-BPG.pdf [last access: 11/08/2018]
 - [24] IMI. *WEB-RADR: Recognising Adverse Drug Reactions*. [Online]. Available from: <https://web-radr.eu/> [last access: 11/08/2018]
 - [25] HALMED. *Open (v.0.2.66.0)* [Online], Available from: <https://open.halmed.hr/client/#/login> [last access: 08/28/2018]
 - [26] SCOPE Work Package 4 ADR Collection, *Increasing Awareness of National Adverse Drug Reaction Reporting Systems: Best Practice Guide*. [Online], Available from: http://www.scopejointaction.eu/_assets/files/WP4.3-Survey-Report-layout-draft-4-final.pdf [last access: 11/08/2018]
 - [27] Central Health Information System of the Republic of Croatia (CEZIH). [Online], Available from: <http://www.cezih.hr/> [last access: 11/08/2018]
 - [28] Ministry of Health of the Republic of Croatia. Zdravstvene ustanove u Republici Hrvatskoj. Retrieved August 9, 2018, from <https://zdravlje.gov.hr/arhiva-80/ministarstvo-zdravlja/zdravstvene-ustanove-u-republici-hrvatskoj/656>
 - [29] European Medicines Agency. *EudraVigilance*. [Online]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000679.jsp&mid=WC0b01ac05800250b5 [last access: 11/08/2018]
 - [30] Y. Moride, F. Haramburu, A. A. Requejo, and B. Begaud. (1997) "Under-reporting of adverse drug reactions in general practice." *British Journal of Clinical Pharmacology*, vol. 43, issue 2, pp. 177-181, Feb. 1997, doi: 10.1046/j.1365-2125.1997.05417.x
 - [31] R. M. Martin, K. V. Kapoor, L. V. Wilton, and R. D. Mann, "Underreporting of suspected adverse drug reactions to newly marketed ("black triangle") drugs in general practice: an observational study." *BMJ*, vol. 317, issue 7151, pp. 119-120, July 1998. [Online]. Available from: <http://www.bmj.com/content/317/7151/119> [last access: 11/08/2018]
 - [32] Official Journal of the European Union. *Directive 2010/84/EU of the European Parliament and of the Council* [Online], Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2010_84/dir_2010_84_en.pdf [last access: 11/08/2018]

- [33] Heads of Medicines Agencies. *A Strategy for the Heads of Medicines Agencies, 2011-15*. [Online]. Available from: http://www.hma.eu/fileadmin/dateien/HMA_joint/02-HMA_Strategy_Annual_Reports/02-HMA_Strategy_Paper/2010_12_HMA_StrategyPaperII.pdf [last access: 11/08/2018]
- [34] HALMED. *Adverse Drug Reaction Report for 2016* [Online]. Available from: http://www.halmed.hr/fdsak3jnFsk1Kfa/ostale_stranice/Izvjesce-o-nuspojavnima-za-2016.pdf [last access: 11/08/2018]
- [35] I. Ribeiro-Vaz, A. M. Silva, C. Costa Santos, and R. Cruz-Correia, "How to promote adverse drug reaction reports using information systems – a systematic review and meta-analysis." *BMC Medical Informatics and Decision Making*, vol. 16, issue 27, Mar 2016, doi:10.1186/s12911-016-0265-8 [Online]. Available from: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4772685/#> [last access: 11/08/2018]
- [36] Agencia Española de Medicamentos y Productos Sanitarios (AEMPS). *Portada La AEMPS*. [Online]. Available from: <https://www.aemps.gob.es/laAEMPS/portada/home.htm> [last access: 11/08/2018]
- [37] Medicines and Healthcare products Regulatory Agency (MHRA). *About us*. [Online]. Available from: <https://www.gov.uk/government/organisations/medicines-and-healthcare-products-regulatory-agency/about> [last access: 11/08/2018]
- [38] Netherlands Pharmacovigilance Centre Lareb. Available from: <https://www.lareb.nl/en/> [last access: 28/08/2018]
- [39] ISB 1582 Electronic Yellow Card Reporting' standard. Available from: <http://www.isb.nhs.uk/documents/isb-1582> [last access: 28/08/2018]
- [40] SNOMED International. *SNOMED CT*. [Online]. Available from: <https://www.snomed.org/snomed-ct> [last access: 11/08/2018]
- [41] MedDRA MSSO. *MedDRA. Medical Dictionary for Regulatory Activities*. [Online]. Available from: <https://www.meddra.org/> [last access: 11/08/2018]
- [42] eHDSI MVC. *WHO ICD-10 The International Statistical Classification of Diseases and Related Health Problems 10th Revision*. [Online]. Available from: <https://ec.europa.eu/cefdigital/wiki/display/EHSEMANTIC/WHO+ICD-10+The+International+Statistical+Classification+of+Diseases+and+Related+Health+Problems+10th+Revision> [last access: 11/08/2018]