OPeN:

Linking the National Adverse Reactions Database with Clinical IT Systems in Croatia

Arian Rajh, Dubravka Sudic, Katarina Gvozdanovic
Agency for Medicinal Products and Medical Devices
Zagreb, Croatia
e-mail: {arajh, dsudic, kgvozdanovic}@halmed.hr

***Abstract*— The Croatian Agency for Medicinal Products and Medical Devices is in the middle of implementation of project "OPeN." With its completion, the Agency will automate capturing of pharmacovigilance data from various clinical Information Technology (IT) systems and enable data syndication in the Croatian National Adverse Reactions database. The mechanism can consequently help healthcare professionals to avoid repeated input of data and save their time; this way, it will enhance medical practice and improve the public health system in Croatia.**

Keywords*— *Adverse Drug Reactions; Clinical Information Technology Systems; National Adverse Reactions Database; OPeN; Pharmacovigilance.

I. INTRODUCTION

The Agency for Medicinal Products and Medical Devices (HALMED) [1] is the National Competent Authority (NCA) in charge of the regulation of medicinal products and medical devices in Croatia. Its post-approval activities include monitoring of pharmacovigilance. "Pharmacovigilance is the science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem." [2] An Adverse Drug Reaction (ADR) is a noxious and unintended drug effect [3]. HALMED is responsible for the maintenance of the national ADR database.

Pharmacovigilance (PhV) is principally a data-driven discipline. The database contains all ADRs received from various sources in Croatia. There were many advances in the last decade related to pharmacovigilance in general and ADR reporting in a particular degree.

Although spontaneous reporting is a "valuable resource for detecting actual drug-drug interactions" [4], the global PhV community has recognised the problem of underreporting [5]. That led to taking regulatory actions, as reported in European Medicines Agency's publications [6]–[8], as well as international guidance [9], further prescribed by international specifications [10] [11]. It also led to the use of technological innovations like data mining [12] [13] or other IT techniques, and finally to conducting standardisation efforts in the field [14]–[16]. One way to mitigate the problem of underreporting is to get, or to mine, large quantities of data [17]. Another and additional way to do it is to add relevant [18] input from health professionals into the reporting process and to increase the quality of data.

To enhance its pharmacovigilance capacities, HALMED participated in international pharmacovigilance IT projects – "Strengthening Collaboration for Operating Pharmacovigilance in Europe Joint Action" (SCOPE) and "WEB-Recognising Adverse Drug Reactions" (WEB-RADR). The SCOPE project, a joint action at European Union (EU) level, focused on the development of reporting mechanisms for ADRs [19]. It resulted in several IT-related recommendations related to facilitation of data collection/syndication and processing in various systems. Croatia, Netherlands, and United Kingdom developed mobile apps for reporting ADRs under WEB-RADR in 2015 and 2016 [20].

HALMED gained experience through these international projects and initiated a new project called "OPeN." [24] OPeN conformed entirely to the third suggestion of *Work Package 4* of project SCOPE, namely its recommendation to NCAs to "integrate suspected ADR reporting into clinical IT systems" [21].

The goal of the OPeN project was to increase both the number and the quality of ADR reports and to facilitate the communication between Health Care Professionals (HCPs) and NCAs via connected clinical IT systems and national ADR databases.

This paper describes the development of HALMED's OPeN system. In Section II, we describe risks related to the OPeN project, as well as project phases and methods of system development. In the same section, we describe modules of the system and its use. In Section III, we discuss why and how certain pharmacovigilance mechanisms were included in efforts taken by HALMED during the past decade, as well as in the OPeN project itself. We explain the advantages of direct reporting and the gist behind HALMED's project. We also outline examples of equivalent European projects, selected for study because they use mechanisms of direct ADR reporting from clinical systems. Despite the fact that they were examined before the development of HALMED's own system, we would nevertheless like to highlight some features like integration or communication with other systems, as well as coding and data mapping abilities. In Section IV, we show expected benefits of the OPeN project for Croatian public health system. Finally, Section V announces future work on the project, adding a goal to further facilitate the Croatian health sector.

 ISBN: 978-1-61208-618-7

II. METHODS OF THE DEVELOPMENT

A. *Project risks, phases, and the development*

Establishing a system as complex as OPeN involves many different institutions and stakeholders (The Ministry of Health of the Republic of Croatia, The Croatian Health Insurance Fund, The Croatian National Institute of Public Health, and providers of IT solutions and services in the healthcare domain). The most significant risk in this entire process is ensuring the necessary funding, as well as coordinating activities of various stakeholders, on time. Within the extent of the OPeN project, it was planned to connect OPeN with the Central Health Information System of the Republic of Croatia (CEZIH) [22], as well as with different hospital IT systems. However, this was not yet accomplished, and HALMED's staff is actively working to achieve it. A possible risk related to this integration attempt could be the circumstance that the operation of CEZIH is not within the remits of HALMED (the responsibility lies with The Croatian Health Insurance Fund). Another risk is related to the fact that there are 64 hospitals in Croatia: they have various levels of computerisation and use various IT solutions. HALMED has developed the OPeN system to the extent that it is functionally ready; however, other Croatian main stakeholders need to incorporate it into the national healthcare ecosystem. The ideal path would be to enforce providers to incorporate ADR reporting elements into their clinical software products, but a variety of approaches are applicable for solving communication issues between the systems.

The whole software development consists of central modules development, establishing the connection of the system to its environment, and specific modules development (see Figure 1). At the moment, HALMED has finished the first phase of system's development and the project is entering the second phase. The first phase dealt with the facilitation of HALMED's internal ADR processing and the development of Web reporting form and smart PDF form. The result of the first phase is a functional Web ADR reporting form and completed OPeN ingest functionality. The interface of the OPeN system is user-friendly and designed to both simplify and decrease the time required for the data entry. During the reporting, HCPs can select values in fields from various lists of medicinal products, institutions, units, and measurements. Users can also choose one of the existing templates for new reports.

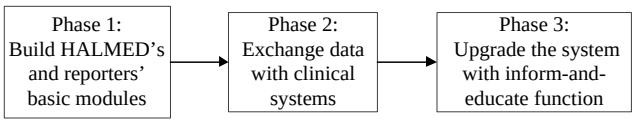

Figure 1. OPeN's system development phases.

B. *The OPeN system modules, functionalities and use*

HALMED has developed OPeN 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 in HALMED). OPeN has been based on the Windows technology and developed in .NET Framework, while the data is stored in the Microsoft Structured Query Language server database (MS SQL). Firewall and Secure Sockets Layer (SSL) protocol protect the entire system. Access and data protection are established through the domain admin policies for internal users (Windows Active Directory) and the ones for external users. Backup procedures are performed regularly. HALMED's goal with this project was to automate reporting of adverse drug reactions by the HCPs directly via IT systems they use at their workplace. The scenario is the following: HCP submits reports and transfers them to HALMED, where the staff in charge of this task can process them (see Figure 2).

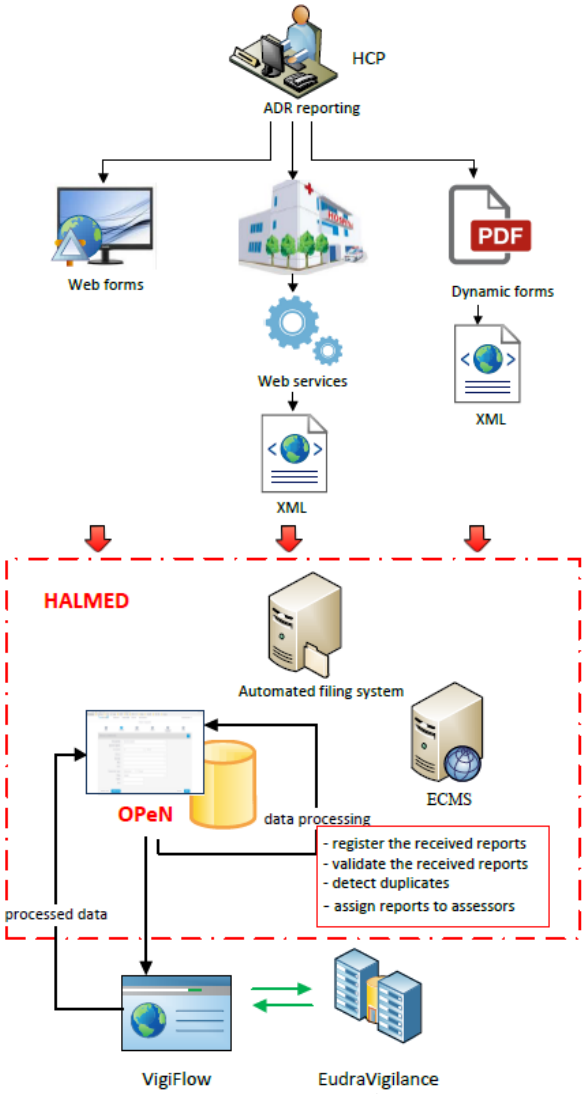

Figure 2. OPeN's workflow

The design of OPeN predicts connecting the system with CEZIH (Central Health Information System of the Republic of Croatia) and also with all IT systems used by HCPs, like hospital systems, general practitioners' IT systems, systems in pharmacies, private practices, and some additional stakeholders' systems. Most of the data required for reporting ADRs are already contained within HCPs' IT systems, so it takes less time to fill out the forms; it simplifies the process of sending data to HALMED as well. All things considered increase the quality of sent data, reduce the possibilities of errors during data entry, and prevent the submitting of the incorrect or incomplete forms.

The Web part of OPeN consists of two modules: the module for HALMED's employees and the module for external users (HCPs). Figure 3 shows OPEN's data entry interface (with creation dates and statuses - "Received" or "Task accepted"). HALMED's employees use the system to register the received reports, to validate them, to detect duplicates, to assign them to assessors, to track their processing, and any further steps (e.g., sending them to EudraVigilance system [23]). The module for HALMED's employees is also connected to HALMED's 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 during the entire process. External users (HCPs) will use the system to report adverse drug reactions, having registered with the purpose of authentication.

All institutions that participate in data exchange will use the same list of HCP authentication data. This facilitates data exchange without the need for additional authentication at the moment of sending the data to HALMED. A common list will enable data traceability. Data exchanged between internal and external systems will be in XML data format. XML structures are following E2B-R2 and E2B-R3 formats [10] [11]. In the first phase of the project, HALMED has developed a smart PDF form which also includes embedded lists. The form is available via HALMED Website and OPeN system Website, currently in the test phase [24]. Anyone can access the form, fill it out and send it via e-mail. OPeN contains the function of automatic data loading from the form into the OPeN database, which eliminates the requirement to enter data manually.

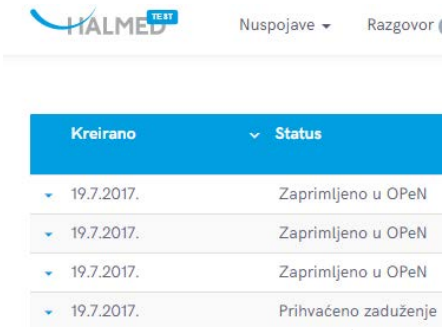

Figure 3. OPeN's data entry interface

III. DISCUSSION

A. *Efforts to increase the number and quality of ADRs in Croatia during 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 systems' capacity in detecting drug safety issues. ADR systems are reliant upon the goodwill of HCPs and patients, not only on identifying suspected ADR reports, but also on reporting them. ADR reporting schemes are recognised to be subject to underreporting [25]–[27]. Directive 2010/84/EU, which came into force in 2013, identified the issue and stated that NCAs need to encourage and improve reporting of ADRs. According to the 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" [28]. Heads of Medicines Agencies (HMA) within their *Strategy* for 2011-2015 have further propagated the aim of the Directive [29]. HMA aimed to support the strengthening of spontaneous ADR reporting systems, indicating four main complementary approaches as a mean to improve ADR reporting and achieve a more robust national pharmacovigilance system: (1) education, (2) motivation, (3) promotion, and (4) facilitation of ADR reporting, all of them mainly directed to HCPs and patients.

Throughout the last decade, HALMED has been included 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, bringing Croatia into top ten countries in the world per number of ADRs per million inhabitants [30]. Education, motivation, and promotion have been extensively used and combined with different ways of facilitation of reporting. The facilitation was done by introducing novel methods for capturing ADRs: online reporting form for patients and mobile app for patients and HCPs. On-line reporting form was launched in 2012: by 2016, 20% of all ADRs were received through this channel. Although HALMED intended the on-line reporting form for patients, it was widely used by HCPs. The PhV mobile app was introduced in 2016 (through project WEB-RADR) and it accounted for the 2% of ADR received in 2016. The focus was on activities aimed at facilitation of reporting. HALMED started introducing electronic reporting and it influenced the rationalisation of internal ADR processing. The main reason was a reduction of manual entry into the national ADR database. This issue gained more importance as the increasing number of received ADRs began to have a real impact on resources available to other pharmacovigilance processes within HALMED (e.g.,

 ISBN: 978-1-61208-618-7

assessments of risk management plans, periodic update safety reports).

B. Direct reporting from clinical systems as advancement in the field of pharmacovigilance

Although regulatory workload in HALMED increased substantially from 2013 onwards, there was still an active commitment to improving the national PhV system, as well as possibilities to detect signals and potential safety issues. This was this 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 the quality of ADR reports. The way to do it is by capturing ADR reports from online reporting form and clinical systems. The idea behind OPeN was to build a system that will allow the communication of 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 reporting efficacy of HCPs by reducing their efforts to complete forms as it uses data from patients' records and automates data entry methods. HALMED considers it as a way of promotion of ADR reporting in general. According to the systematic review and meta-analysis published by I. Ribeiro-Vaz et al. [31], projects that aim to promote ADR reporting by using IT represent an increasing trend. According to their aggregate analysis, these interventions doubled the number of captured ADR reports.

Reporting from clinical system helps obtain complete information on ADRs. It can significantly facilitate case assessment by providing context for ADRs. An additional value is the possibility to prompt reporters to complete a report within the system when specific tasks are completed, e.g., drug withdrawal from therapy. It can also prompt a reporter to enter data that are more particular into the report (e.g., a batch number in case of ADR related to vaccines and biologicals). This information is rarely captured in paper ADR form; it can, however, be crucial for understanding the cause of the ADR.

An additional benefit of automatic data entry method in direct ADR reporting from a clinical system is the use of controlled data entry. Where applicable, ADR reporters could use data registries (e.g., medicinal product registry) to facilitate their data entry method. Another benefit of using IT is the option to use data validation rules and to facilitate receiving accurate and valid reports. In this way, national ADR databases are becoming more accurate too. It reduces the need to contact the reporter in case of non-valid ADRs. Rules of reporting should meet the applicable ICH E2B standards [10] [11] and minimum required data. Additional validation rules should also be built in if needed to meet business or regulatory needs. Besides, the use of dictionaries, including the mapping of dictionaries, should help set up standardised terminology and coding terms for assessors. The use of dictionaries would represent a significant benefit for any pharmacovigilance system. The second phase of OPeN will address these issues.

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

According to the SCOPE results, there are only 2 NCAs that use the possibility of capturing ADRs from clinical systems: regulatory agencies from Spain and UK (Agencia Española de Medicamentos y Productos Sanitarios – AEMPS, Medicines and Healthcare products Regulatory Agency - MHRA) [32] [33]. Their systems are mainly set to retrieve ADRs from General Practitioners (GPs), and this decision is logical since they have access to most of the patients' health information. Although their systems differ, their experiences indicate that the integration of ADR reporting with electronic health records, primary care, and e-prescription systems is positively correlated with the increased quantity of ADR reports and the quality of information received. In the UK, for example, during the pilot phase in 2011, automatic ADR reporting feature was added to one primary care system for GPs (SystemOne). Analysis of received Yellow Cards showed an increase for GP ADR reports of almost 50% compared to 2010. The UK and Spanish systems have 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 Farmacovigilancia Española, Datos de Reacciones Adversas (FEDRA), but have to pass through their regional PhV centers. Also, the ADR description is in the form of free text, while the UK system allows ADRs to be coded using *The Systematized Nomenclature of Medicine* (SNOMED) dictionary [34]. The MHRA has built up a mapping between SNOMED concept terms and *Medical Dictionary for Regulatory Activities* (MedDRA) [35] which is standard terminology used for coding ADRs worldwide. It enables ADR reports to be automatically loaded into the MHRA's PV database without the need to code ADRs. OPeN will allow direct upload of ADR reports to the national database, however, coding of ADRs by the reporter will not be possible.

HCPs in Croatia use International Statistical Classification of Diseases and Related Health Problems 10 (ICD 10) terminology for coding medical terms [36] and no mapping to MedDRA is available. In addition to this, OPeN will allow for two-way communication with the reporters, mainly for retrieving follow-up information. We believe this is the benefit of our system, although no information on the communication possibilities within the UK or Spanish systems is widely available. There is limited published information on the particular data elements of both systems; we were able to compare our systems solely by actively participating in the SCOPE project. However, the information on the systems might be outdated since the SCOPE includes data up to 2013. Also, it is challenging to detect the publication on the efforts of other countries in

 ISBN: 978-1-61208-618-7

implementing ADR reporting from clinical systems. As per our knowledge, Netherlands is piloting such a system. Previous research of the systems outlined above helped HALMED's team to avoid straggling in the development, implementation, and fine-tuning of the OPeN system.

IV. CONCLUSIONS AND EXPECTED BENEFITS

Submissions of timely and well-completed ADR reports increase the data available to NCAs and their capacity to protect public health in the end. It improves NCAs' ability to detect, identify, investigate, and act on potential drug safety issues.

Pharmacovigilance professionals consider the integration of clinical IT systems and ADR databases as bleeding edge tool for increasing both the number and the quality of captured ADRs. HALMED initiated OPeN for this very reason. Croatian NCA started with the initiative that aimed for the integration of the national ADR database, CEZIH, and various hospitals IT systems. Expected benefits include:

- Facilitation and promotion of ADR reporting,
- A higher number and better quality of reports,
- Reduction of manual data entry and data processing time per report,
- Standardisation, clarification of professional terms, dictionaries,
- Introduction to analytics, advancement in tracking Key Performance Indicators (KPI) and signals, planning for BI features,
- Sophisticated and proactive protection of public health.

V. FURTHER WORK

An efficient and connected health system and its components facilitate the protection of patients, efforts of HCPs, and beneficial activities of all other stakeholders in the national health domain. The OPeN system is an excellent example of the vital technological element of the national health system. Although Web-application OPeN is fully functional, HALMED is working on signing the protocol with the Croatian National Institute of Public Health to enable data exchange between these key health sector institutions. The system can become fully operational on a national level only after strengthening this cooperation. In the meantime, the Ministry of Health of the Republic of Croatia inserted activities related to OPeN into one of their strategic goals for 2019. Besides, concurrently with the signing of data protocol and with preparing for the second phase, HALMED is planning the third phase (see Figure 1) or system upgrade with the additional module that will cover informing and online education of HCPs.

REFERENCES

[1] Agency for Medicinal Products and Medical Devices of Croatia. *About HALMED.* [Online], Available from: http://www.halmed.hr/en/O-HALMED-u/ [last access: 03/01/2018]

[2] 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: 01/30/2018]

[3] 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.

[4] 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

[5] L. Hazell and S.A.W. 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

[6] 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: 01/30/2018]

[7] 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: 01/30/2018]

[8] 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: 01/30/2018]

[9] 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.

[10] 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: 01/30/2018]

[11] ICH E2B(R3). *Individual Case Safety Report (ICSR) Specification and Related Files*. Available from: http://www.ich.org/products/electronic-standards.html [last access: 01/30/2018]

[12] 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

[13] 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

[14] European Medicines Agency. *Substance, Product, Organisation and Referential (SPOR) master data.* [Online]. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulati

on/general/general_content_000645.jsp&mid=WC0b01ac058078fbe2 [last access: 01/30/2018]

[15] ISO/HL7 27953-1: 2011 Health informatics – Individual Case Safety Reports (ICSRs) in pharmacovigilance – Part 1: The framework for adverse event reporting

[16] ISO/HL7 27953-2: 2011 Health informatics – Individual Case Safety Reports (ICSRs) in pharmacovigilance – Part 2: Human pharmaceutical reporting requirements for ICSR

[17] 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

[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] 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: 01/30/2018]

[20] IMI. *WEB-RADR: Recognising Adverse Drug Reactions.* [Online]. Available from: https://web-radr.eu/ [last access: 01/30/2018]

[21] 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: 01/30/2018]

[22] Central Health Information System of the Republic of Croatia (CEZIH). [Online], Available from: http://www.cezih.hr/ [last access: 03/01/2018]

[23] 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: 01/30/2018]

[24] HALMED. *Open (v.0.2.66.0)* [Online], Available from: http://open-test.halmed.hr/client/#/login [last access: 01/30/2018]

[25] 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

[26] 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: 01/30/2018]

[27] Hazell L. and Shakir SAW. (2006) "Under-Reporting of Adverse Drug Reactions A Systematic Review." Drug Safety 29(5): 385-39

[28] 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: 01/30/2018]

[29] 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: 01/30/2018]

[30] HALMED. *Adverse Drug Reaction Report for 2016* [Online], Available from: http://www.halmed.hr/fdsak3jnFsk1Kfa/ostale_stranice/Izvjesce-o-nuspojavama-za-2016.pdf [last access: 01/30/2018]

[31] 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: 01/30/2018]

[32] 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: 03/01/2018]

[33] 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: 03/01/2018]

[34] SNOMED International. *SNOMED CT.* [Online]. Available from: https://www.snomed.org/snomed-ct [last access: 01/30/2018]

[35] MedDRA MSSO. *MedDRA. Medical Dictionary for Regulatory Activities.* [Online]. Available from: https://www.meddra.org/ [last access: 01/30/2018]

[36] eHDSI MVC. *WHO ICD-10 The International Statistical Classification of Diseases and Related Health Problems 10th Revision.* [Online]. 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: 01/30/2018]

 ISBN: 978-1-61208-618-7