Riassunti delle relazioni finali dei progetti di ricerca svolti dagli studenti nell'ambito del tirocinio formativo del master per l'anno accademico 2017-2018

Monitoring of adverse reactions from vaccine within ASL Novara and on the National territory

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ABSTRACT

Introduction: Vaccines are biological medicinal products, whose aim is to prevent one or more infectious diseases by stimulating the immune system and the consequent acquisition of so-called active immunity. The activities related to the collection, evaluation, analysis and communication of Adverse Events Following Immunization (AEFI) and any other problem inherent to vaccinations, are called Vaccine vigilance. It is therefore a useful tool for constantly monitoring the efficacy and tolerability of vaccines, even after approval and marketing.

Aims: To identify vaccines subject to the highest number of adverse reactions as reported in a three-year period (2016-2018); to evaluate the most common adverse reactions; to estimate the influence of the variable "sex" in the onset of these ADRs in ASL Novara (ASL NO) and to compare these data with the national data from National Pharmacovigilance Network (RNF) in the same period.

Methods: We searched the RNF database for adverse reactions related to vaccines using the keyword "J07" based on the ATC classification, in the time period from 01/01/2016 to 31/12/2018. We then compared the results from ASL NO and the national territory using System Organ Class (SOC) classification.

Results: Comparison of the collected data showed that both in ASL NO and on the national territory, Bexsero was the vaccine with the most spontaneous reports. The most represented items from SOC classification were "General disorders and administration site conditions", "Skin and subcutaneous tissue disorders" and "Nervous system disorders". The variable "sex" was found to be irrelevant.

Conclusions: Vaccines are an invaluable resource for protection of individual and collective health. Despite of the reduction of ADRs reports within ASL NO, an increase of AEFI reports was found. The breakdown of AEFI reports by year shows a relevant increase farther to entering in to falls of the law 119/2017 which established some vaccinations as mandatory. The bigger amount of recorded reactions is referred to as "General disorders and administration site conditions" follow with by "Skin and subcutaneous tissue disorders" and "Nervous system disorders". Pyrexia is the PT for the most AEFI report. This is the most common AEFI and it is also found in RCP of most vaccines as common and frequent ADR. Therefore, the future goals could be to draw the attention of physicians to the importance of reporting suspect AEFI to vaccines to the local Pharmacovigilance manager not only if rare or uncommon, but also when already known and found on the vaccine's RCP.

Keywords: Pharmacovigilance, Vaccine, Vaccine vigilance, Adverse reactions, AEFI, RNF, ASL NO.

Drug-Drug Interaction in analgesia and sedation: new guidelines update for pediatrics

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ABSTRACT

Introduction: Pediatric Intensive Care Units (PICUs) are critical settings, where fragile patients are treated, thus requiring quick and precise medical decisions. Moreover, since children are often more sensible to pain and discomfort deriving from medical procedures, analgesia and sedation are frequently necessary. Therefore, a combination of several drugs is required, thus increasing the chance of drug-drug interactions (DDIs). Furthermore, as children cannot be considered as "little adults", it is important to carefully consider the pediatric pharmacokinetics (PK), which importantly differ from that of adult patients.

Aims: The main objective of this work has been the analysis of DDIs arising from the combined use of different sedo-analgesic drugs in the context of PICUs. Moreover, the PK profile of these medications has been considered. In particular, understanding the issues related to DDIs and pediatric PK may help to a better use of sedo-analgesic drugs in children, thus reducing the chance of adverse events (AEs).

Methods: Two main databases for DDIs has been screened for interactions between sedo-analgesic drugs. In particular, Terap (Istituto Mario Negri) has been considered for the Italian scenario, whether Clinical Pharmacology database has been used to take into account the interactions occurring between drugs marketed in the United States. Nevertheless, the database considered, DDIs has been divided into three main classes, namely "contraindicated/severe", "major" and "moderate". Concerning the PK profile of sedo-analgesic drugs, Clinical Pharmacology has been the main source of information. Moreover, the SmPC of each medication has been carefully examined, thus allowing a comprehensive collection on all the available information. Lastly, literature research using PubMed database has been performed to fully elucidate the DDIs and PK profiles.

Results and Conclusions: Previous release of pediatric sedo-analgesia guidelines has been considered for determining which drugs have to be examined. Among the different classes of medications, opioids display the highest number of DDIs, thus they should be used with more attention than other drugs. Moreover, the database and literature search has shown that there is poor information about the pediatric PK profile of the majority of drugs considered. Our analysis, however, clearly demonstrated that information about DDIs and PK profile is essential in the PICU clinical practice. Lastly, the data acquired through this work may be useful for integrating the clinical information for the update of guidelines for sedo-analgesia in pediatrics.

Keywords: Drug-drug interactions (DDIs), Pediatrics, Sedation, Analgesia, Pharmacokinetics, Adverse events, Clinical practice, Guidelines.

The oversight plan in the management of market research service providers: analysis of the impact of its introduction on the performance and quality of the third parties

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ABSTRACT

Background: Today, organizations often choose to provide certain activities to service providers or partners. In these situations, the need for well-defined and coordinated working relationships increases. The concept of Oversight Plan is born, which defines the management, control and supervision of outsourced activities. For contracts with an impact on pharmacovigilance, the oversight plan outlines the supervision mode of the vendor's performance in recognizing and reporting any safety data to the company according to defined timing and to certain quality standards.

Aim: As part of the management of market research providers, this project aims to analyse how the introduction of a dedicated oversight plan has had an impact in improving the performance and quality of service providers, also from a point of view of reporting adverse events more punctual and precise.

Methods: Sample and systematic quality checks of the reports and of the original material collected by the service provider during the activity were carried out. The deviations concerning the sending of reconciliations (CTV) and reports of adverse events (AE) were delayed and the non identification of AEs (missed AEs) by service providers detected in a period between 2015 and 2018.

Results: The deviations referred to the sending of CTV and AE delayed increased between 2015 and 2016 and then decreased in 2017 and disappeared in 2018. The deviations due to missed AE instead appeared in 2016 and increased in 2018. The Oversight Plan aims at the reduction and minimization of these types of deviations.

Conclusions: From this project emerged the importance of the Oversight Plan in improving the performance of service providers, in particular in recognizing and quickly reporting the safety data to the company.

Keywords: Pharmacovigilance, adverse events - AE service provider, outsourcing, oversight plan, market research, patient support program, deviations, CAPA.

Quality analysis of adverse drug reaction observed in Lombardy during 2018

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ABSTRACT

Introduction: The purpose of this study was to evaluate how effectively the quality management of Adverse Drug Reactions (ADRs) system established by the Lombardy Pharmacovigilance Regional Center (CRFV) is being carried out according to the national Guidelines for CRFVs.

Objective: The tasks assigned by AIFA to the CRFV include the quality control of the cards included in the RNF, with particular reference to the completeness and accuracy of the data, as reiterated by the operating procedure of 16 July 2018, the purpose of this analysis was to verify the efficiency of the reporting system by the Lombardy CRFV in 2018, in terms of the number of incomplete/incorrect data sheets, missing/incorrect data types and the time trend of both indicators (between 2018 and 2017).

Methods: Lombardy reports regarding serious ADRs entered into the National Pharmacovigilance Network (RNF) from January to December 2018 were checked on a monthly basis and evaluated for data completeness and accuracy (i.e. encoding of ADR according to MedDRA standard terminology, severity criteria, outcome and follow-up of the ADR, suspected drug). The analyses were performed by using the VigiSegn application.

Results: During the study period, Lombardy entered 13361 reports into the RNF (+46.5% compared with 2017), 6164 of which regarding serious ADRs (46% of the total, +67.94% compared with 2017). After 12 month-period of CRFV evaluation and subsequent involvement of Local Heads of Pharmacovigilance (LHPV) in completing and correcting reported information, the percentage of complete cards increased from 22.02% in 2017 to 36.25% in 2018 of the total insertion cards. Missing data on suspected drugs also were reduced: dosage (from 18% to 14%), therapeutic indication (20%-10%), taken actions (32%-20%), rechallange (65%-42%); start and end date of therapy (respectively: 27%-24%, 39%-36%), outcome (30%-12%).

Conclusions: Through the collaboration of CRFV and LHPV during the study period the quality of serious ADR reports has clearly improved, contributing to ameliorate the safety profile of drugs and making potential alarm signals about ADRs faster and easier identifiable.

Keywords: CRFV, National Pharmacovigilance Network (RNF), ADR (Adverse Drug Reaction).

Safety profile of antibiotic therapy in pediatric population: an exploratory study using the pharmacovigilance database of the Lombardy Region

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ABSTRACT

Background: Ensuring appropriate antibiotic prescription is an urgent public health and patient safety priority, as excessive use and misuse has led to the development of resistance to antibiotics, which is a growing health and economic threat. In order to contain this phenomenon, it is important to intervene from early childhood. The European Medicines Agency issued a new guideline on Good Pharmacovigilance Practices (GVP) in the pediatric population (EMA/572054/2016) on 8 November 2018. This provides Pharmacovigilance tools and processes to address the needs and specific challenges of the pediatric population. There is a considerable amount of scientific information regarding the onset of antibiotic related adverse reactions in the pediatric population, even though no national and regional data are available.

Aim: To propose a descriptive analysis of antibiotic-related adverse reactions in the pediatric population, focusing on the off-label use, medication error (when prescribing, dispensing, administering and on assumption), abuse and misuse.

Methods: We selected and analyzed all reports of Lombardy Region in which children were involved (0 <18 years) recorded in the RNFV from the 1st January 1990 to the 06th June 2018, using the data warehousing application VigiSegn. The reports usually contain information about the patient (age, sex), medications (suspect and concomitant), ADR, severity, medication error, outcome, healthcare structure and entry year of the ADR.

Results: 2,990 ADR reports were recorded in Lombardy: 14.08% of reports retrieved were classified as serious and pharmacological interactions accounted for 0.2%. The average age was 5.7 years. Amoxicillin/clavulanic acid is the drug most implicated in the ADRs (47.87%) and urticaria is the most significant ADR (33.9%), followed by rash (13.5%), itching (10.5%). Out a total of 2,990 analyzed cases, 6 were pharmacology interactions (0.2%), 6 abuse (0.2%), 27 therapeutic errors (0.9%), 6 overdose (0.2%), 6 off-label use (0.2%) and 80 cases of therapeutic inefficacy (2.3%).

Conclusion: Data on serious reports highlight the need to closely monitor this pediatric therapeutic area to ensure a safe and appropriate use of antibiotics.

Keywords: Pediatrics, Antibiotics, ADRs, Children.

Signal detection method in a pharmaceutical company: performance and impact on workload across spontaneous reporting databases

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ASTRACT

Background: Signal detection is the process of looking for and/or identifying signals using data from any source and it is performed by the European Medicines Agency (EMA), National Competent Authorities (NCAs) and Market Authorization Holders (MAHs). Traditional methods of signal detection are supported by statistical disproportionality methods allowing a standardized prioritization of Drug-Event Combinations (DECs) to be further evaluated. The company's safety database and EudraVigilance (EV) are two of the main sources of data available to MAHs to identify new signals. Since 22 February 2018 MAHs of the active substances included in pilot phase have to monitor them in EV and inform EMA and NCAs of validated signals with their medicines.

Aim: In this study, we proposed a signal detection method aimed to screen EV and the Company's DSMS, focusing on the identification of SDRs, which need further investigation and we speculated on the possible implementation of EV screening as future requirement for all marketed products.

Methods: We retrieved data from the Chiesi Farmaceutici S.p.A. DSMS (Oracle Argus) and EudraVigilance in the form of line listings and electronic Reaction Monitoring Report (eRMR), aggregated at DEC level. We analyzed data of twenty-three (23) products, basing the selection on Company's active ingredients available in EVDAS, from 01 August 2018 to 31 January 2019. We calculated the total proportion of known ADRs that were identified as SDR (sensitivity) and the total proportion of SDRs that corresponds to known ADRs (i.e. precision or positive predictive value or PPV) for both datasets.

Results: A total of 448 SDRs originated from the Company's DSMS, out of which 103 matched with a known ADR. 985 SDRs originated from the eRMR analyses, out of which 187 matched with a known ADR. The overall precision in the DSMS (0.23) resulted higher than in EVDAS (0.19) whereas the workload was 21.2% higher in the EVAS screening than in the DSMS. The DSMS screening resulted 43.6% more sensible than the one performed in EVDAS.

Conclusion: In our study, screening of EV data showed not only lower overall performance than screening the DSMS, but also higher workload. We obtained evidence that screening the DSMS with the proposed method would not compromise the detection of true signals. On the other hand, it probably comes with an organisational increased workload when compared with "traditional" methodologies like the manual review of data. An even bigger workload increase is expected with the implementation of the eRMR screening for all marketed products in the routine signal detection process. EV data of products not involved in the pilot phase could be used to support the outcomes of the DSMS screening as additional source of information to the signal validation, together with literature, clinical and preclinical data, known class effect and clinical relevance.

Keywords: Signal detection, EudraVigilance data analysis system (EVDAS), Pharmaceutical Company, Sensitivity, Precision.

How do Marketing Authorization Holders deal with the recording of information of suspected adverse reactions from EudraVigilance? State of the art and future perspectives

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ABSTRACT

Background: Since the launch of the new EudraVigilance on 22 November 2017, the entire Pharmacovigilance system has been facing great changes. According to the new legislation, Marketing Authorization Holders (MAHs) shall not report to National Competent Authority (NCA) but directly to EudraVigilance. As regards the download of Individual Case Safety Report (ICSRs) from EudraVigilance by MAHs, it does not require to set filters for active substance or medicinal product as all ICSRs for medicinal products registered by MAHs in the EVXMPD/Art.57 are included. As a result of the simplified reporting, a huge amount of information become available to MAHs. Whilst this represents a significant progress in Pharmacovigilance, it deeply impacts on the sustainability of the work, requiring a re-organization of the ICSRs management system.

On July 12th 2018 European Medicines Agency (EMA) released a note for clarification in order to address questions by MAHs about their obligations to collect suspected adverse reactions for substances of medicinal products for which they have a Marketing Authorization in the European Economic Area (EEA) and to which they access through EudraVigilance. According to this Note, MAHs are not obliged to record ICSRs which have been submitted by other MAHs to EudraVigilance but they have to comply with their pharmacovigilance system.

Aims: The aim of this project is to evaluate the impact and sustainability of not recording information on suspected adverse reactions which have been submitted by other MAHs in EudraVigilance, unless they contain as co-suspect drug a medicinal product registered by a client company.

Methods: Download of ICSRs from EVWEB is based on the EudraVigilance Access Policy L2A. "All organization types" is set as filter for the Sender Organization Type during the daily download, thus including all ICSRs. Currently Asgenia is approaching a new method that consists in monitoring the download of ICSRs registered in EudraVigilance by NCA separately from the download of ICSRs registered in EudraVigilance by other MAHs (i.e. Non-National Competent Authorities, Non-NCAs). Furthermore, Asgenia is monitoring closely ICSRs submitted by other MAHs to EudraVigilance and which contain as co-suspect drug a medicinal product registered by a client company.

Results: the results obtained from the daily monitoring of ICSRs downloaded from EudraVigilance show the significant workload associated with case management of ICSRs submitted by Non-NCAs. Furthermore, the potential risk associated with loss of ICSRs should be estimated if Asgenia processed only ICSRs containing as co-suspect drug a medicinal product registered by a client company from those submitted from Non-NCAs.

Conclusion: Whilst the significant advantages in terms of burden of works, it is still to be understood together with the client companies to what extent this can affect their own pharmacovigilance activities.

Keywords: EudraVigilance, National Competent Authorities, Marketing Authorization Holders, GVP module VI, Pharmaceutical Companies.

A pharmacovigilance study on the safety profile of HPV vaccines in the male population: data from US Vaccine Adverse Event Reporting System (VAERS)

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ABSTRACT

Background: Human Papilloma Virus is one of the most common sexually transmitted infection, responsible of cervical cancer, anal cancer, cervical intraepithelial neoplasias and genital warts. It affects both men and women. To date three HPV vaccines are available: Gardasil®, Gardasil9® and Cervarix®. The aim of this project was to contribute to the analysis of the safety profiles of HPV vaccines in the male population.

Methods: We reviewed all the reports of Adverse Events Following Immunization (AEFI) reported in the US Vaccine Adverse Event Reporting System (VAERS) from January 2006 to September 2018. We focused on males aged 6-29 years. The analysis was performed using the Reporting Odds Ratio (ROR) with 95% confidence (CI95%) interval and p value ≤0.05, as statistical parameter to evaluate vaccine-event pairs distribution.

Results: A total of 5,493 reports of AEFI were retrieved in the database. Of these, 354 were serious. The AEFIs more reported and statistically significant experienced by males were: syncope (N=701, ROR= 2.85, CI95% 1.414-5.757), loss of consciousness (N=425, ROR=2.79, CI95% 1.358-5.718), fall (N=272, ROR= 3.54 CI95% 2.003-6.265), immediate post-injection reaction (N=208, ROR=3.40, CI95% 1.877-6.158), presyncope (N=122, ROR= 4.13, CI95% 2.513-6.779) and dyskinesia (N=104, ROR= 2.90, CI95% 1.447-5.817). Others AEFIs reported were nausea, vomiting, fatigue and hyperhidrosis. ADRs reported in males and females resulted to be similar. All ADRs are listed and reported in the Summary of Product Characteristics (SmPC) of the corresponding vaccine.

Conclusions: The HPV vaccines were generally well tolerated in men. Despite government recommendations and the favourable vaccine safety profile, HPV vaccination coverage is still low. It's necessary to spread a positive approach to immunization. The extension of HPV vaccines to males will probably help to prevent more HPV-related cancers in both females and males.

Keywords: Adverse Events Following Immunization, Human Papilloma Virus, Men, Vaccinovigilance.

The reporting gap: incomplete information for DataEntry and case evaluation

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ABSTRACT

Background: Continuing post-marketing drug surveillance accompanied by risk minimization of developing harmful and unintended reactions to drugs is the main objective of Pharmacovigilance. Firstly, the implementation of this project depends on the collection and monitoring of suspected adverse drug reaction reports, which represent the starting point to provide useful information about the risk profile of medicinal products and their impact on patients' lives.

Aim: The purpose of this project is to highlight how often the reports are incomplete, lacking important information that would allow an appropriate assessment of the link in causality between drug exposure and reaction and therefore appropriate case assessment. A report can be valid only if it presents the four minimal requirements: identifiable reporter, identifiable patient, adverse reaction and suspect drug. However, the quality of information is determined not only by the presence of these elements but also by data consistency, completeness and the precision with which it is reported.

Methods: An important role in the management of the reports is performed by Marketing Authorization Holders that are required to have an organization that ensures the acquisition of safety information and its subsequent evaluation. To this end the DataEntry activities, namely of entering of safety information into a corporate database, are essential to flag new signals of side effects or new elements about already noted side effects. These activities consist in the compilation of system sheets with the information contained in the source documents. Specifically, these concern the source of the report and reporter, the patient, adverse reaction and description of the event. Nevertheless, more detailed data, representing the foundation for a proper assessment of the case are the temporal correlation between drug intake and reaction, action taken with the suspect drug and the presence of dechallenge and rechallenge, in most cases are unavailable or cannot be known.

Results: With DataEntry, it is clear how often it is difficult to obtain all the details concerning a specific case. More and more frequently, reports are processed that bring no information relevant to the temporal correlation of the drug-event, nor in relation to the suspension or re-administration of the medical treatment to the patient.

Conclusion: For reports to become useful and give information that is valuable both for the patient and the producer it is fundamental to improve the quality of data provided. For this reason, it is important to raise awareness and if necessary activate pharmacovigilance projects that orient all the actors involved towards appropriate signalling.

Keywords: Individual Case Safety Reports and Literature Reports, DataEntry, Causality Assessment, Quality of information.

Drug tolerance in major depressive disorder treatment with SSRIs and SNRIs

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ABSTRACT

Background: Major depressive disorder (MDD) affects 300 million patients and is one of the most disabling illnesses worldwide. There are several efficacious drugs for the pharmacological treatment of MDD which show a similar efficacy profile. The treatment of MDD can involve several problems such as the onset of adverse drug reactions (ADRs), lack of response to the treatment and tolerance to a previously effective drug.

Aim: The aim of this study was to investigate cases of therapeutic failure to discriminate between drug inefficacy and drug tolerance of selective serotonin reuptake inhibitors and serotonin-noradrenaline reuptake inhibitors.

Methods: Data were extracted from American FAERS database from 2004 to 2015. We collected Individual Case Study Reports of patients in treatment with SSRIs and SNRIs as the only suspect active pharmaceutical ingredient (API), indicated for MDD, which resulted in therapeutic failure. Drug tolerance has been identified using the duration of the pharmacological treatment calculated based on treatment start date and reaction date.

Results: The number of ICSRs where drug tolerance term was correctly used was 3 (0.37%) versus real number of drug tolerance of 316 (39.21%). 177 reporters were healthcare professional. SSRIs requested a greater treatment duration than SNRIs to develop drug tolerance (1410.45 ± 1546.71 days versus 879.28 ±1080.12 days)

Conclusion: Tolerance to antidepressant is a common problem, difficult to discriminate even for healthcare professionals. SSRIs could be better than SNRIs for the maintenance treatment of MDD because of the longer treatment duration needed to achieve a tolerance to the pharmacological treatment.

Keywords: MDD, drug tolerance, antidepressants, SSRIs, SNRIs, FAERS, Pharmacovigilance.

Implementation of safety variation: how to ensure a correct management. The experience of an Italian service provider company

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ABSTRACT

Background: Product information (PI) safety variation is a change of the terms of a marketing authorization. The variations could be requested by regulatory authorities (national or international), during the assessment process of a regulatory practice (variation, renewal), or after cumulative assessment procedures (PSUR, referral etc.) or they could be spontaneously proposed by QPPV/MAH. In accordance with Article 16 of Regulation 726/2004 and Article 23 Directive 2001/83/EC, the Marketing Authorization Holder(s) are required to keep the product information up to date with the current scientific knowledge, including the conclusions of the assessment and recommendations made public by means of the European medicine web-portal and/or the CMDh webpage. According to the Commission Regulation (EC) n. 1234/2008 of the European Commission, the Marketing Authorization Holder(s) must submit variations to the Competent Authority (CA) whenever necessary and/or required.

Aim: In order to submit safety variations, the Pharmacovigilance department performed a periodic screening of specific websites. The purpose of this project was to implement a workflow for the management of safety variation for medicinal products for human.

Methods: We compiled a Standard Operating Procedure (SOP) to define in detail the process and the action to be taken from the search of requests to the implementation of the safety variation (in compliance with the EU Pharmacovigilance requirements), from the point of view of a pharmacovigilance service provider/contract organization. The identification of the potential sources of PI safety variation was the key point for the implementation of a correct SOP.

Results We present a submission of a safety variation for a specific medicinal products containing Propofol, following the screening of the CMDh website on 5th October and covering the period of September 21st, 2018 - October 4th, 2018, as a result of a correct implementation of the SOP.

Discussion: Monitoring of medicinal products safety variations is necessary to promote and protect public health and to enhance patient safety. The implementation of the SOP was successful and has proved it compliance al local and European procedures.

Keywords: Safety variation, Screening, Referral, Standard Operating.

A practical approach to the monitoring of worldwide scientific literature in pharmacovigilance

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ABSTRACT

Background: Pharmacovigilance is the set of activities relating to the detection, assessment, understanding and prevention of adverse effects or any other drug-related problem, in order to guarantee a favourable benefit/risk ratio for the population. To facilitate the work of the Marketing Authorization Holder (MAH), in 2015 the European Medicine Agency (EMA) introduced a monitoring system called Medical Literature Monitoring (MLM) service. EMA has the task of monitoring the selected medical literature for a defined list of active ingredients used in medicinal products and to provide MAH all suspect adverse reaction collect in the relevant period. According to the guidelines, however, this monitoring is not sufficient. In fact, every MAH are required to monitor at least two sources to guarantee complete coverage.

Objective: To assess the positive aspects and issues of literature monitoring, paying particular attention to the problem of duplicates and the impact that this activity has in the daily work of the pharmacovigilance officer.

Methods: Description of how the worldwide literature monitoring is managed by FIDIA, distinguishing the literature cases to be inserted in database from those that are not, but necessary for Periodic Safety Update Report (PSUR) and/or Signal detection.

Results: During the literature monitoring it has been noticed how with the introduction of the MLM service many daily activities have been simplified, thus facilitating the work of the pharmacovigilance officer. At the same time, however, some issues have emerged that have not yet been resolved such as the problem of duplicates or the fact that the company has to do a double-check monitoring because MLM service covers only a percentage of active substances, thus increasing the time needed to carry out the complete monitoring.

Keywords Monitoring of Literature, MLM service, Reactions weekly, PubMed, ADRs, Duplicates, ICSR.

Evaluation of the management ability of adverse events during clinical trials: survey exploring the efficacy of reporting guidelines among site staff

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ABSTRACT

Background: Monitoring the safety of medicines is a continuous process starting from the earliest clinical studies and extending throughout the post-marketing period. The overall aim of Pharmacovigilance is to monitor and protect safety of subjects and patients exposed to medicinal product during development phase and after marketing approval has been granted.

Pharmacovigilance activities in pre-marketing clinical trials and in the post-marketing can be contracted out to independent drug safety experts within a contract research organization (CRO). To ensure the well-being and the safety of patients, who are at the centre of the clinical trial, all the actors of the clinical research, such as the sponsor, the CRO, and the site staff, collaborate and work together. Therefore, it is important to ensure timely detection of adverse events because safety data influence clinical care of subjects.

Objectives: The main aim of my project is to investigate how adverse event's reports are managed during clinical trials by site staff and monitors. Moreover, information on the cultural background of investigators, their knowledge in the field of the ADR reporting, as well as their approach to this activity, have been collected, in order to have a comprehensive view of the issue.

Methods: A questionnaire consisting of 8 multiple-choice questions has been elaborated and sent to 45 IQVIA Clinical Research Associates. The eight multiple-choice questions of the questionnaire have been drawn up in Italian language and all participants were native Italian speakers.

Results. The results confirm a general compliance of the site staff in the notification of adverse event and an overall positive attitude in following guidelines when dealing with adverse events. The overall effectiveness in the notification of adverse events during clinical trials suggests the good applicability of ICH's guidelines to the real clinical practice.

Conclusions: This study represents a preliminary framework that could be periodically used to identify strengths and weaknesses of AEs reporting standard procedures. Given the presence of the limitations highlighted by the results, future research should point towards the involvement of larger samples, possibly addressing the survey also to the medical staff, in order to have additional viable perspectives. Moreover, the questionnaire should be formulated by taking into account the objectivity bias, hence a scale of measurement that could lead to more statistically different answers should be elaborated.

Keywords: Contract Research Organization, adverse events reporting, GCPs, site staff, safety.

EVDAS (Eudravigilance Data Analysis System) - il nuovo strumento per la signal detection

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ABSTRACT

Background: In the last couple of years, the European pharmacovigilance system underwent deep and significant changes. In particular, on 22 November 2017, the European Medicines Agency (EMA) launched a new version of Eudravigilance, with enhanced functionalities, needed to support the significant changes introduced by the European pharmacovigilance legislation in terms of requirements for reporting suspected adverse reactions. Within this new system, EMA enabled Marketing Authorisation Holders (MAH) to access to the EudraVigilance Data Analysis System (EVDAS). EVDAS has been designed to allow users to analyse safety data collected in EudraVigilance, enabling better-informed decisions about the safety profile of medicinal products and, above all, providing signal detection tools.
Aim: the aim of this thesis is to compare the results, in terms of safety data, obtained with the classical signal detection (case-by-case) to the new EVDAS signal detection approach, underlying the main differences and trying to give an explanation to them.
Method: The first half of 2018 has been considered. In this period, firstly, a classical signal detection regarding the drug (X) through a case-by-case method has been carried out: describing scientifically all listed and unlisted cases obtained from the EudraVigilance database, analysing safety data obtained by the screening of literature and social media and merging that information with the analysis of the sales data of X compared to previous years. Regarding the EVDAS signal detection, first it has been done the access to the platform through the QPPV's credentials. Then, the time interval for the analysis of data has been selected choosing the Ad-hoc option and the active principle substance (X) has been selected from the provided list. Subsequently, the e-RMR file has been downloaded and the ADR occurred were collected. At this point, it was possible to obtain the statistic value (calculated as ROR) and the list of possible signals was collected. Last, a comparison between these ADRs (statistically considered as possible signals by EVDAS) and the ADRs founded in the safety database of the company (Y) has been made. For the ADRs, which matched with those obtained from EVDAS, a clinical evaluation to validate the signal has been carried out.
Results and conclusions: Considering our study, the comparison, between the classical signal detection (case-by-case) and EVDAS, does not show any particular difference in terms of safety data and results obtained. Although we did not get new potential safety signals, EVDAS represents a step forward in the present and future of performing a signal detection for pharmaceutical companies.

Keywords: Signal-detection, Case-by-case, EVDAS, EMA, ROR.