AN INNOVATIVE APPROACH TO PHARMACOVIGILANCE

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To my parents

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Abstract

Pharmacovigilance (PhV) plays an important role in safeguarding patient safety and appropriate use of medicines by monitoring adverse drug reactions (ADRs). The monitoring of ADRs following marketing approval of a drug is crucial for identifying previously undetected, rare, or serious side effects. Underreporting of ADRs remains a barrier for ADR monitoring.

The aim of the study was to assess healthcare professionals (HCPs) knowledge, attitude, practice, barriers and need for more education about ADR reporting and to identify tools to empower and motivate them to participate in PhV activities.

The study was divided into 4 parts: 1) Review of individual case safety reports (ICSRs) received by the Malta Medicines Authority (MMA) from 2004 until 2019. 2) Setting up of three focus groups with HCPs from different settings (academia, hospital, regulatory). 3) Development, validation and dissemination of a questionnaire disseminated to pharmacists, medical doctors, nurses and dentists to assess knowledge, attitude, practice, barriers and need for more education on ADR reporting. 4) Development, validation, dissemination and evaluation of two educational webinars on *Pharmacovigilance in the time of a pandemic crisis – Adverse Drug Reaction reporting* Part 1 (Background, ADR reporting system, Case studies) and Part 2 (COVID-19 vaccination - current situation, Case studies, Outcomes of ADR reports, Recognising ADRs in practice).

Results: 1) The number of ICSRs sharply increased from 29 (2007) to 194 (2010), and from 118 (2016) to 223 (2018). 2) The focus groups pointed out the need for quantifying the extent and reasons for underreporting. 3) The mean knowledge score deduced from the questionnaire for HCPs (374) was 44/50, pharmacists (44/50); medical doctors (43/50), dentists (42/50), nurses (39/50) ($p < 0.001$). HCPs on a Likert scale 1 to 5 agreed

that reporting an ADR was important for medicinal products' safety and patient care (4.87) and that ADR reporting was part of their duty as HCPs (4.81) ($p<0.001$). Out of the HCPs who encountered an ADR (65.8%, n=246), 30.1% (n=74) and 23.6% (n=23.6) almost never or rarely reported the event, respectively, claiming difficulty in understanding whether the ADR has occurred (50.0%; n=187) and ADRs being already known and documented (43.9%; n=164). HCPs agreed that they require more education on ADR reporting (strongly agree: 40.4%, n=151; agree 31.8%, n=119), through continuing professional education seminars (65.8%; n=246). 4) The evaluation forms were completed by 103 out of 132 HCPs (first webinar), and 73 out of 90 HCPs (second webinar). Nurses agreed that the educational webinar made them more aware of the importance of ADR reporting (first webinar 4.85, $p=0.039$; second webinar 4.71, $p=0.031$) and that it helped them to overcome barriers toward ADR reporting (first webinar 4.70, $p=0.047$; second webinar 4.76, $p=0.031$). Nurses agreed more than other HCPs with the idea of the Safety Representative (4.88; $p=0.024$).

It is postulated that HCPs were knowledgeable and had a positive attitude towards ADR reporting and yet they admitted to not reporting ADRs. The main reason stated for not reporting was difficulty to understand whether an ADR occurred, followed by ADRs being already well known and documented to occur. HCPs agreed to receiving more education and training about ADR reporting.

Educational webinars, such as the ones conducted in this study, helped increase and improve awareness on the importance of quality ADR reporting which could lead to better PhV practices which can positively impact patient care and patient quality of life.

Keywords: adverse drug reaction reporting; barriers; education and training; knowledge; pharmacovigilance; underreporting

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List of Abbreviations

ADR	Adverse Drug Reaction
DHPC	Direct Healthcare Professional Communication
EMA	European Medicines Agency
GVPs	Good Pharmacovigilance Practices
HCPs	Healthcare Professionals
ICSRs	Individual Case Safety Reports
MAH	Marketing Authorisation Holder
MMA	Malta Medicines Authority
NCA	National Competent Authority
PASS	Post-Authorisation Safety Study
PAES	Post-Authorisation Efficacy Studies
PhV	Pharmacovigilance
PRAC	Pharmacovigilance Risk Assessment Committee
RMMs	Risk Minimisation Measures
SmPC	Product's Summary of Product Characteristics
WHO	World Health Organisation

Chapter 1

Introduction

1.1 The importance of Pharmacovigilance

Pharmacovigilance (PhV) is defined by the European Medicines Agency (EMA) as the "science and activities relating to the detection, assessment, understanding and prevention of adverse effects or any other medicine-related problem".[1] Some of the activities carried out by the post-marketing surveillance are: monitoring the use of medicinal products when used in normal conditions to detect previously unrecognised adverse effects; continuous review of benefit-risk profile of medicinal products on the market in order to decide what action to take, if necessary; providing information to healthcare professionals (HCPs) and patients with the goal of optimising the safe and effective use of medicinal products (Borg et al, 2011).

PhV has evolved during time (Fornasier et al, 2018). The event which marked the beginning of PhV history was the death of a young girl in 1848 after receiving chloroform as anaesthetic. After the young girl's death, The Lancet Journal established a commission which exhorted English doctors to report any death by anaesthesia (Routledge, 1998). In 1955 acetylsalicylic acid was shown to cause gastrointestinal disorders, and its use was avoided in patients suffering from peptic ulcers (Levy, 1987).

The event which led to a shift in PhV activities was related to the use of Thalidomide in 1961. While prescribed during pregnancy, as an antiemetic or as a sedative, thalidomide was seen to increase congenital malformations of babies from 1.5 to 20%, (McBride, 1961). After the event of thalidomide, the first European pharmaceutical directive was developed. Directive 65/65/EEC1 aimed to harmonised standards for the approval of medicinal products within Europe.[2] In 1968, the World Health Organisation (WHO)

[1] European Medicines Agency [Internet]. Amsterdam: Pharmacovigilance: Overview; [cited 2021 Jan 31]. Available from: https://www.ema.europa.eu/en/human-regulatory/overview/pharmacovigilance-overview
[2] The Council of the European Economic Community [Internet]. Brussels: Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action

programme for International Drug Monitoring was established and ten countries took part in the programme. The WHO programme for International Drug Monitoring aimed to develop an world-wide collaboration to detect unrecognised adverse drug reactions (ADRs) not reported during clinical trials (Edwards et al, 2003). In 1992 the European Society of Pharmacovigilance was instituted and later was renamed to International Society of Pharmacovigilance (IsoP). IsoP aimed to promote PhV and enhance medicinal products safety.[3] In 1995 the EMA was established and in 2001 the official European database for collecting information on suspected ADRs, EudraVigilance, was created (Fornasier et al, 2018).

In 2012 the Directive 2010/84/EU was issued and brought changes in European PhV, such as modifications in defining ADRs.[4] The new legislation also included the Good Pharmacovigilance Practices (GVPs), a set of measures to support the performance of PhV activities in Europe. GVPs apply to medicinal product authorised centrally as well as nationally.[5]

Other changes that the Directive 2010/84/EU brought were: participation of patients in PhV activities, consolidation of the EudraVigilance database, possibility to impose Post-Authorisation Safety Study (PASS) or Post-Authorisation Efficacy Studies (PAES) for medicinal products already on the market and institution of the Pharmacovigilance Risk

relating to medicinal products; [cited 2021 Feb 1]. Available from: https://www.echamp.eu/eu-legislation-and-regulation-documents/directive_65-65-eec_-_consolidated_version.pdf

[3] International Society of Pharmacovigilance [Internet]. London: About ISoP - ESOP/ISoP History; [cited 2021 Feb 1]. Available from: https://isoponline.org/about-isop/esopisop-history/

[4] European Commission. Directive 2010/84/EU of the European Parliament and of the Council of 15 December 2010 amending, as regards pharmacovigilance, Directive 2001/83/EC on the Community code relating to medicinal products for human use [Internet]. Official Journal of The European Union. 2010; L 348/74-99 [cited 2021 Feb 10]. Available from: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2010_84/dir_2010_84_en.pdf

[5] European Medicines Agency [Internet]. Amsterdam: Good pharmacovigilance practices; [cited 2021 Jan 31]. Available from: https://www.ema.europa.eu/en/human-regulatory/post-authorisation/pharmacovigilance/good-pharmacovigilance-practices

Assessment Committee (PRAC).[4] In November 2017, the new EudraVigilance system was released and new obligations regarding signal management and reporting of suspected ADRs for marketing authorisation holders (MAHs) were outlined. MAHs were given access to the EudraVigilance database to fulfil Pharmacovigilance obligations. MAHs had to submit Individual Case Safety Reports (ICSRs) to EudraVigilance, instead of to the National Competent Authority (NCA), had to monitor data available in EudraVigilance and inform EMA or a NCA of any new signals identified. EMA had to submit ICSRs through EudraVigilance to the WHO Uppsala Monitoring Centre, rather than NCAs doing this.[4]

1.2 Adverse Drug Reactions

An ADR is defined by the Directive 2001/83/EC as "a response to a medicinal product which is noxious and unintended".[6] The new definition of ADR included in the Directive 2010/84/EU specifies that ADRs may occur with use of medicinal product within or outside the terms of marketing authorisation. Conditions of use of the medicinal product outside the marketing authorisation include: off label use, overdose, misuse, abuse and medication errors.[4] The Directive 2001/83/EC defines a serious ADR as "an adverse reaction which results in death, is life-threatening, requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability or incapacity, or is a congenital anomaly/birth defect".[6]

The risk of ADRs is intrinsic to all drugs and is linked to different factors, such as dose, frequency of administration and genetic characteristics. The risk for arising ADRs is also associated to pharmacokinetics of different populations, such as paediatrics, elderly and

[6] European Commission. Directive 2001/83/EU of the European Parliament and of the Council of 6 November 2001 on the Community code relating to medicinal products for human use [Internet]. Official Journal of the European Communities. 2001; L 311/67-128 [cited 2021 Apr 13]. Available from: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32001L0083&from=EN

patients with hepatic or renal problems (Sultana et al, 2013). Ayalew et al in his literature review showed that the development of an ADR was linked to polypharmacy, especially in elderly people who are most likely to take more than one medication. Geriatric populations and patients taking multiple medications were also more subjected to be hospitalised because of ADRs (Ayalew et al, 2019). ADRs may have a negative effect on both the clinical practice and the economic aspect (Sultana et al, 2013).

ADRs are one of the leading causes of morbidity, mortality and poor therapeutic outcomes (Khalil et al, 2020). The percentage of patients admitted to the hospital because of an ADR ranged from 0.5 to 12.8% (Bouvy et al, 2015) and was 15% in another study (Ayalew et al, 2019); while the frequency of ADRs leading to hospital admission in children ranged from 2.1% to 5.2% (Sultana et al, 2013). The percentage of patients who developed an ADR while hospitalised ranged from 1.7 and 50.9% (Bouvy et al, 2015).

Globally, the proportion of ADRs with a fatal outcome ranges from 0.1% to 10%, whereas in developed countries the proportion ranges from 0.05% to 3% (Hailu and Mohammed, 2020). It is estimated that ADRs cause around 197,000 deaths in Europe annually (Hadi et al, 2017). Around 2.7% of ADRs occurred in elderly were fatal (Ayalew et al, 2019); while up to 39% of ADRs occurred in paediatrics could be life-threatening or result in death (Sultana et al, 2013).

ADRs increase hospital admissions and health care costs. In the United Kingdom, ADRs prolong hospitalisation of about 8 days and cost approximately 706€ million per year (Formica et al, 2018). Results from a more recent systematic review showed that the cost per patient hospitalised due to an ADR ranged from 702€ to 7,318€ (Batel et al, 2016). In the United States, ADRs are the fourth to the sixth leading cause of death and the cost was estimated to be up to 30.1 billion dollars per year. Costs of ADRs may include:

hospitalisation due to an ADR, prolongation of hospital stay due to an ADR, additional clinical investigations and prescription cascades as a consequence of the prescription of a new treatment to treat conditions that may be due to another medication (unrecognized ADR) (Sultana et al, 2013).

1.3 The importance of Adverse Drug Reaction reporting

Before authorisation, information about safety and efficacy of medicinal products newly developed is limited to the results from animal testing and clinical trials. Studies in animals are sometimes not sufficiently predictive of human safety while clinical trials are limited by: sample size, duration and the environment. The sample size of a clinical trial consists of a selected population. The duration of clinical trials is limited for a period of time. The environment where clinical trials are performed is controlled and it differs from the conditions of use encountered in normal clinical practice. Information about rare but serious ADRs, chronic toxicity, use in special populations (i.e.: children, pregnant women and elderly people), or drug interactions (i.e.: drug-drug, drug-food, drug-food supplement) may be incomplete or not available (Borg et al, 2011).

When new medicinal products enter the market, they may be used in a larger population, for a longer period of time and in concomitance with other drugs. Certain adverse events, especially the ones with low frequency, may emerge with widespread real-world use of medicinal products.[1] The limited data on safety and efficacy of newly developed medical products underlines the need for post-marketing surveillance. (Borg et al, 2011).

Following increasing concerns about ADRs and withdrawal from the market of certain medicines (Raine et al, 2012), pharmacovigilance has changed from being a “passive” activity, where interventions take place following ADRs, to a “pro-active” activity which aims to detect early signals from both clinical trials and post-marketing surveillance to

identify risks with use of medications and to minimize harm.[7] NCAs and MAHs have to maintain vigilance on medicinal products by law.[4] The process of continuous monitoring for safety concerns is a core objective of PhV (Borg et al, 2018). PhV plays an important role in safeguarding patient safety and appropriate use of medicines, by monitoring ADRs (Santoro et al, 2017). The monitoring of ADRs following marketing approval of a drug is crucial for identifying previously undetected, rare, or serious side effects (Martin et al, 2004).

1.4 Adverse Drug Reaction Reporting Systems

ADR reporting represents the cornerstone of PhV and it allows the accomplishment of PhV activities. Through the early detection of new ADRs, ADR reporting helps identify potential signals associated to drugs' use, especially serious events with very low frequency (Palleria et al, 2013).

Spontaneous Reporting System is the main system for identifying previously undetected, uncommon or unexpected ADRs (Ali et al, 2018) as well as continuously assessing the benefits-risk balance of some drugs (Hailu and Mohammed, 2020). With spontaneous reporting system, suspected ADRs are reported voluntarily by HCPs, manufacturers and the patients (Pal et al, 2013). Both HCPs and patients are critical in the success of the national post marketing surveillance by reporting suspected ADRs (Borg et al, 2018). "It shall be the duty of doctors and other healthcare professionals to immediately report to the Authority any suspected adverse reaction to a medicinal product in Malta" is what the Maltese legislation on PhV indicates.[8] Reporting suspected ADRs helps warn NCAs of

[7] Il Pensiero Scientifico Editore [Internet]. Roma: La farmacovigilanza: storia ed esperienze nazionali e regionali; [cited on 2020 Jan 22]. Available from: https://pensiero.it/files/pdf/migliorare_sicurezza_chemio/capitolo1.pdf

[8] Legislation Malta. Subsidiary Legislation 458.35 Pharmacovigilance Regulations [Internet]. Government Gazette of Malta. 2012; 18985:12399 [cited 2021 Apr 14]. Available from: https://legislation.mt/eli/sl/458.35/eng

new or emerging safety concerns and, as a consequence of new signals identified, regulatory actions can be taken (Borg et al, 2018).

The ADR reporting system is an essential component of the Malta Medicines Authority's (MMA) PhV system. The MMA coordinates the PhV system nationally and its mission is to enhance the effective, safe, and rational use of medicinal products.[9] The national ADR reporting system was established in Malta in 2004 and it is consistent with both the European[6] and the Maltese legislation[8] for the regulation of medicinal products. Both the European Directive and the Maltese law directed NCAs to establish a PhV system with the aim to gather information regarding ADRs (Borg et al, 2018).

1.4.1 Information included in the Adverse Drug Reaction reporting form

HCPs and patients should report suspected ADRs:

- Related to all medicines and vaccines, in particular, for new medicinal products and the ones under additional monitoring, all suspected ADRs, including the minor ones; while for well-known drugs, serious expected and/or unexpected suspected ADRs;[10]
- Occurred in special populations, such as: children, pregnant women and elderly;[10]
- Arising from interaction, such as: drug-drug, drug-food, drug-food supplement;[10]
- Associated with drug withdrawals;[10]
- Resulting from overdose or medication error;[10]
- Or as a consequence of lack of efficacy or pharmaceutical defects.[10]

[9] Malta Medicines Authority [Internet]. Malta: Mission and Objectives; [cited 2021 Apr 22]. Available from: http://www.medicinesauthority.gov.mt/missionobjectives?l=1

[10] Couper M. Safety of medicines - a guide to detecting and reporting adverse drug reaction - Why health professionals need to take action [Internet]. WHO; 2002 [Cited 2021 Apr 14]. Available from: http://www.digicollection.org/hss/en/d/Jh2992e/10.html

1.4.2 The Malta Medicines Authority's Adverse Drug Reaction reporting form

Following the amendment of the definition of ADR with the Directive 2010/84/EU[4], a new ADR reporting form was developed and validated (Tanti et al, 2015). With the new EU definition of ADR, other causes of ADR, such as medication errors, are covered. A new reporting form that collected high-quality case information on ADRs and medication errors was developed and validated in 2015. The new reporting form consisted of a single form which captured i) ADR reporting, ii) ADR reporting due to medication errors and iii) medication error reporting not associated with an ADR.[11] The new reporting form improved the previous national ADR reporting form issued by the MMA in 2004 (Tanti et al, 2015).

To encourage ADR reporting, a statement informing the reporters that reporting an ADR does not necessarily mean admission of causality was added. HCPs do not have to be sure that the ADR they are reporting is necessarily caused by a specific medicinal product. The new ADR reporting form includes a section (Section 3) where the reporter's details are provided, information included in this section is destroyed when data is transferred to EudraVigilance (Tanti et al, 2015).

The new ADR reporting form consists of 4 parts: decision tree, section 1, section 2, section 3. The decision tree makes the reporter decide whether he/she is reporting an ADR, an ADR due to a medication error or a medication error. Section 1 is about the reporting of an ADR. In section 2, a medication error can be reported. Section 3 contains the reporter's details (Tanti et al, 2015).

[11] Malta Medicines Authority. [Internet]. Malta: Adverse Drug Reaction Reporting; [cited 2021 Apr 14]. Available from: http://www.medicinesauthority.gov.mt/file.aspx?f=4495

1.4.3 Criteria to be included in the Adverse Drug Reaction reporting form

For the validity of an ADR reporting form, 4 minimum criteria are needed. The 4 minimum criteria are: an identifiable patient (i.e. initials or sex or age); an identifiable reporter (i.e. doctor, pharmacist, dentist, nurse, or other HCPs); a suspected medicinal product; a suspected ADR (Borg et al, 2018).

Besides the four minimum criteria, an ADR report should be as much detailed as possible to help its evaluation (Borg et al, 2018). Date when suspected ADR/s started or stopped (if known); date when suspected medication/s started or stopped (if known); brand name and batch number for biological medicinal products to ensure traceability; information about de-challenge and re-challenge; patient's details, such as past medical history and concomitant drug; laboratory data are information which can facilitate the evaluation of the ADR report. In order to obtain a better causality assessment, good quality of data as well as timely submission are crucial. Good quality of data included facilitates the establishment of causal relations between ADRs and medicinal products and consequently leads to timely regulatory actions (Borg et al, 2018).

To report an ADR, the reporter has to fill in Section 1; while to report a medication error the reporter has to fill in Section 2. If reporting an ADR due to a medication error, both Section 1 and 2 have to be filled in. Section 3, which provides the reporter's details, must be filled in for all the reports because the reporter might be contacted in case of a follow up. At the end of the report, guidance with instructions on how to fill in the form is present (Borg et al, 2018).

1.4.4 Management of reports

The MMA receives the ADR report and validates the ADR case. During the validation of the case, information included is evaluated with a causality assessment (French

imputability method). Causality assessment helps and explains the causal relationship between a medicinal product and the occurrence of an ADR. The causality assessment method actually helps understand whether the ADR was due to that medicinal product or not, and to determine the action to be taken. While doing the causality assessment, the Product's Summary of Product Characteristics (SmPC) of that specific medicinal product is checked to see whether that ADR is listed or not. The procedure will affect the outcome of the causality assessment and the forms are processed in the same way as if the ADR was not listed in the SmPC of that specific medicinal product (Borg et al, 2018).

The reporter is sent feedback and might be asked for a follow up. The ADR report is included in the local database and then transmitted to the EudraVigilance system. During the transmission of the information to EudraVigilance, reporters' details (Section 3) are discarded (Tanti et al, 2015).

1.5 Outcomes of Adverse Drug Reaction reporting

ADR reporting supports other PhV activities and feeds into product pharmacovigilance lifecycle management (Borg et al, 2018). Risk minimisation measures (RMMs) are interventions which aim to enhance the safe and effective use of medicinal products throughout their life cycle, by preventing or decreasing the occurrence of ADRs, or reducing their severity or impact on patients.[12] RMMs aim at providing "the right medicine, at the right dose, at the right time, to the right patient and with the right information and monitoring."[12]

[12] European Medicines Agency [Internet]. Amsterdam; c1995-2020 [cited 2021 Apr 19]. Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2). Available from: Guideline on good pharmacovigilance practices (GVP) - Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2) (europa.eu)

RMMs are divided into two categories: routine risk minimisation and additional risk minimisation measures. Routine risk minimisation applies to all the medicinal products and examples are: package leaflet, SmPC, pack size, product labelling and legal status.[13] Some safety concerns of a medicinal product require additional measures, as a routine approach is not sufficient. When selecting the most suitable RMM, seriousness and preventability of a potential ADR and the action to be taken are considered. Other factors taken into consideration are: indication, route of administration, target population, healthcare setting.[12]

Additional RMMs are measures to understand the risk associated with a medicinal product and the ways in which the risk can be minimised. Educational material with the aim to supplement information in the SmPC and leaflet, such as brochures, checklists, patient alert cards are examples of additional RMMs (Borg et al, 2018). Educational material is targeted to both the HCP and the patients, with a different language of communication. Other additional RMMs include controlled access programs, where some medicinal products are prescribed after a patient is informed and has agreed about a particular risk associated with that therapy. Pregnancy prevention program is a set of interventions which aim at ensuring that a woman is not pregnant while taking a medicinal product which might cause harm during pregnancy.[12]

Direct Healthcare Professional Communications (DHPCs) are communication interventions, in form of a letter, sent by the MAH by post or by email to the HCPs. DHPCs inform the HCPs of the need to take particular actions or adapt their practices

[13] European Medicines Agency [Internet]. Amsterdam; c1995-2020 [cited 2021 Apr 19]. Guideline on good pharmacovigilance practices (GVP) Module V – Risk management systems (Rev2). Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-v-risk-management-systems-rev-2_en.pdf

with regards to a medicinal product.[14] Safety concerns may arise from ADR reporting, clinical trials or studies (Borg et al, 2018). A DHPC can be issued to inform HCPs of: suspension or withdrawal from the market for safety purposes, restriction of use, the arise of a new contraindication, a change in the recommended dose, limitation in availability or discontinuation, when quality problems emerged.[14]

When a safety concern regarding the safe and effective use of a medicinal product on the Maltese market is present, the MMA issues a safety circular. A safety circular is a communication tool (letters), issued by the Malta Medicines Authority, which is addressed to both the healthcare professionals and the patients. A safety circular is issued to inform about withdrawal or suspension from the market for safety reasons of a medicinal product; to communicate any restrictions of use, new contraindications or warnings; when product defects leading to safety concerns are observed; and for endorsement of repurposed medications.[14]

1.6 Underreporting of Adverse Drug Reactions

Spontaneous reporting systems present some limitations, which are primarily associated to underreporting, variable quality of information reported and lack of evidence on drug exposure (Palleria et al, 2013). Since ADR reporting is voluntary, underreporting is considered the main limitation for ADR monitoring (Biagi et al, 2013). Underreporting reduces sensitivity because it underestimates the frequency, thus the impact of an ADR. Underreporting also makes the system more vulnerable to selective reporting, which may introduce major bias (Biagi et al, 2013). One to 10% of serious ADRs are reported (Klika

[14] European Medicines Agency [Internet]. Amsterdam; c1995-2020 [cited 2021 Apr 20]. Guideline on good pharmacovigilance practices (GVP) Module XV – Safety communication (Rev 1). Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xv-safety-communication-rev-1_en.pdf

et al, 2017) and there is no difference between reporting rates in the community and in the hospital setting (Hailu and Mohammed, 2020).

Previous studies showed that the main barriers of HCPs not reporting an ADR were: lack of knowledge, negative attitudes, indifference, lack of motivation, misconceptions, difficulty in accessing the ADR reporting form (Lopez-Gonzalez et al, 2009), fear that the report might be incorrect (AlShammari and Almoslem, 2018), lack of training and of understanding reporting rules (Al Rabayah et al, 2019). The study of Hughes and Weiss on community pharmacists revealed that the barriers encountered by pharmacists when reporting an ADR were not seeing ADRs, uncertainty over what to report, lack of confidence and lack of time (Hughes et Weiss, 2019). Another study showed that the main barrier encountered by pharmacists was lack of cooperation and communication between HCP and patients (Alsaleh et al, 2017).

1.7 Improving number and quality of Adverse Drug Reaction reporting

An analysis of knowledge, attitude, practice, and barriers of HCPs towards ADR reporting may help understand which are the factors associated with underreporting. Studies have shown that there is a correlation between knowledge and attitude and ADR reporting. These studies revealed that an inadequate knowledge about ADRs (Oshikoya et al, 2009; Fadare et al, 2011; Khan et al, 2013; Gupta et al, 2011; Suyagh et al, 2015; Al Rabayah et al, 2019; Hallit et al, 2019; Mulchandani and Kakkar, 2019) and a negative attitude (Herdeiro et al, 2006; Khan et al, 2013; Khan et al, 2015; Shanko and Abdela, 2018) are linked to underreporting.

Since knowledge and attitudes of HCPs are potentially modifiable factors to help improve ADR reporting, educational interventions can fill the gaps in attitude and knowledge of HCPs and increase reporting rates (Lopez-Gonzalez et al, 2009). Increasing knowledge

and attitude about ADR reporting should be the first step to help the reporting of ADRs. Educational interventions about ADR reporting help improve the amount and quality of ADR reports (Herdeiro et al, 2008; Pedrós et al, 2009; Lopez-Gonzalez et al, 2015; Ganesan et al, 2017; Nisa et al, 2018, Cheema et al, 2019). A study by Figueirais et al revealed that the number of ADR reports had an increase of 148% after educational interventions (Figueiras et al, 2006). In the study of Ganesan et al, following the educational intervention, the number of ADR reports doubled compared to pre-intervention (Ganesan et al, 2017).

Studies have shown that educational intervention, such as didactic lectures (Primo and Capucho, 2011; Opadeyi et al, 2019); monthly SMS reminders (Opadeyi et al, 2019); workshops (Primo and Capucho, 2011; Ribeiro-Vaz et al, 2011; Herdeiro et al, 2012; Lopez-Gonzalez et al, 2015); telephone interviews (Ribeiro-Vaz et al, 2011; Herdeiro et al, 2012); distribution of educational material (Herdeiro et al, 2008; Pedrós et al, 2009; Cereza et al, 2010; Johansson et al, 2011; Primo and Capucho, 2011; Ribeiro-Vaz et al, 2011; Herdeiro et al, 2012; Lopez-Gonzalez et al, 2015); repeated sending of emails (Johansson et al, 2009; Biagi et al, 2013); educational outreach visits (Figueiras et al 2006; Gony et al, 2010); periodic educational meeting (Pedrós et al, 2009; Cereza et al, 2010) help improve the knowledge, attitude and practice of HCPs towards ADR reporting and ultimately improve the number and quality of ADR reports.

1.8 The role of regulatory bodies in Adverse Drug Reaction reporting

Directive 2001/83/EU specifies that NCAs have to "take all appropriate measures to encourage doctors and other healthcare professionals to report suspected adverse reactions to the competent authorities".[6] In this contest the MMA has set up campaigns to improve ADR reporting and increase education of HCPs, as well as increase awareness of HCPs on ADR reporting (Borg et al, 2018).

Malta participated in the Strengthening Collaboration for Operating Pharmacovigilance in Europe (SCOPE) project which aimed to evaluate current practices of PhV and develop tools to further improve the skills and capability of HCPs in the PhV network (Radecka et al, 2018). In 2017 an infographic campaign to increase the number of ADR reporting was launched. In 2019 a series of 5 workshops have been conducted by the MMA to educate HCPs on the importance of ADR reporting.

1.9 Aims and objectives

The aim of the study was to assess the knowledge, attitude, practice, barriers and need for education of HCPs about ADR reporting and to identify tools to empower and motivate them to participate in PhV activities.

The objectives were:

- To determine how to improve the number and quality of ADR reporting
- To identify what issues and barriers related to ADR reporting are encountered by HCPs
- To develop, validate and disseminate learning activities for HCPs to improve ADR reporting

Chapter 2

Methodology

2.1 Methodology overview

The study was divided into four parts:

i. Review of ICSRs received by the MMA from 2004 until 2019

ii. Organisation of three focus groups with HCPs from different settings

iii. Development, validation and dissemination of a questionnaire assessing knowledge, attitude, practice, barriers and need for more education of HCPs on ADR reporting (Figure 2.1).

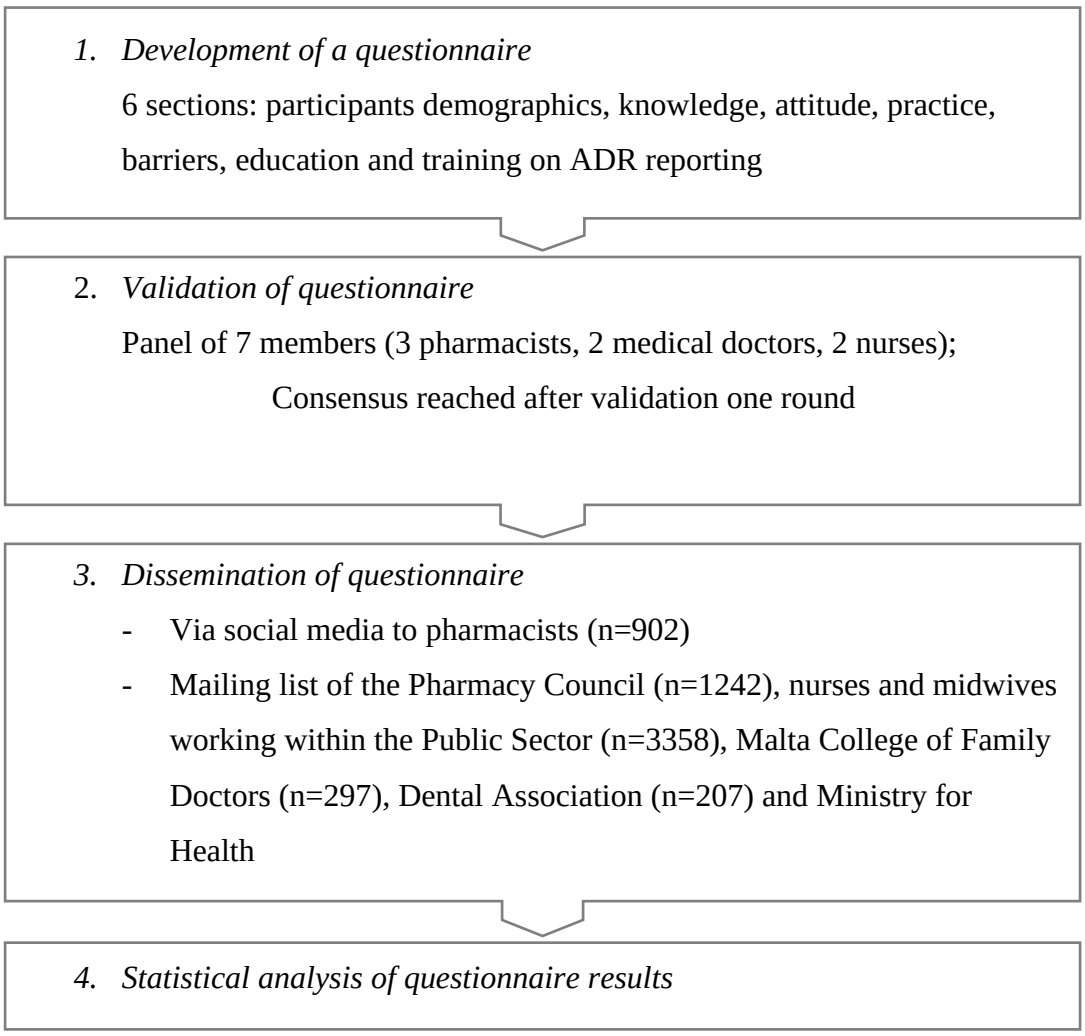

Figure 2.1 Methodology flowchart 1: Assessment of knowledge, attitude, practice, barriers and need for more education of HCPs on ADR reporting using a questionnaire

iv. Development, validation and dissemination of educational material on ADR reporting and evaluation with evaluation form (Figure 2.2).

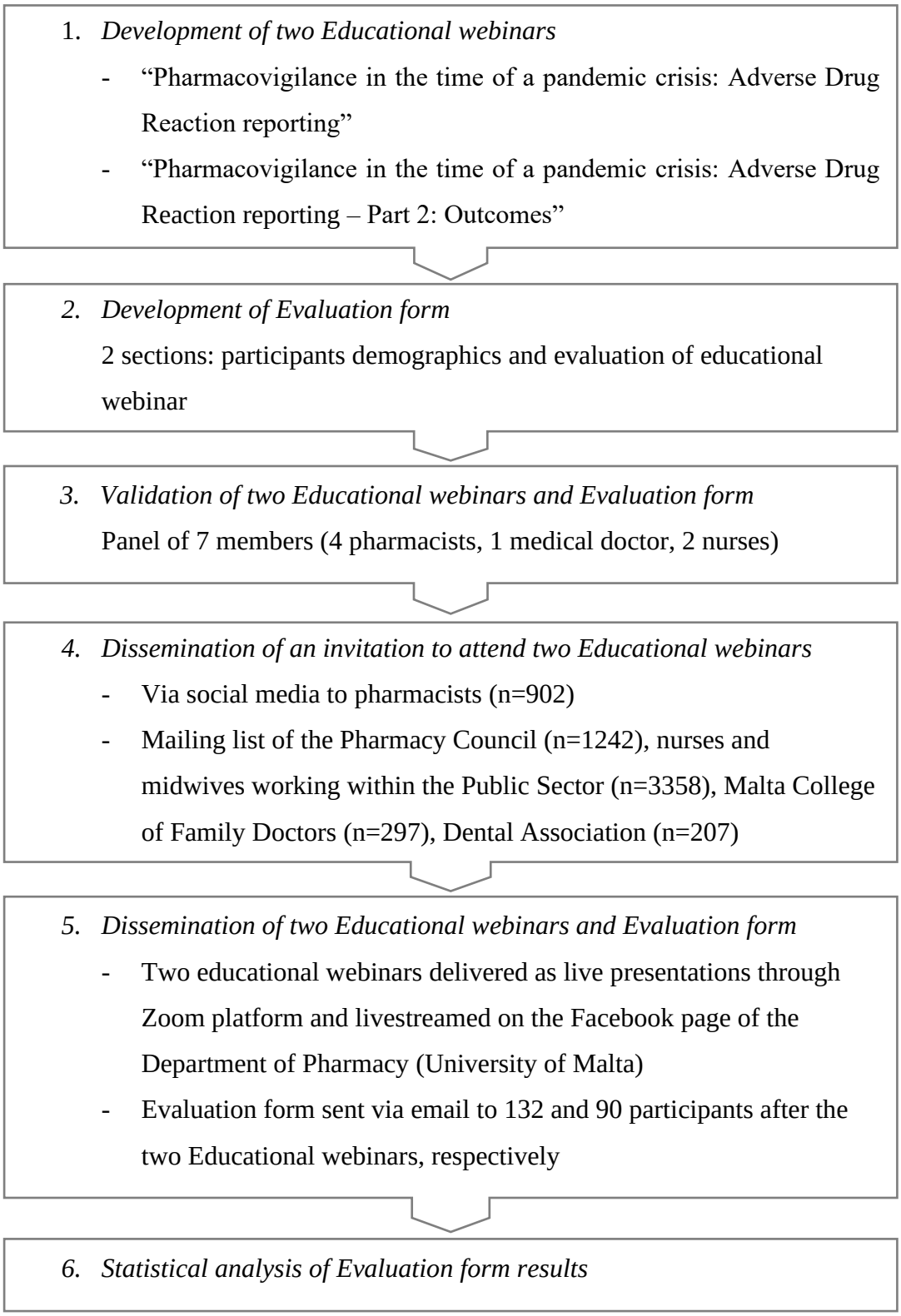

Figure 2.2 Methodology flowchart 2: Development, validation, dissemination and evaluation of educational material among HCPs

2.2 Review of Individual Case Safety Reports received by the Malta Medicines Authority

The annual reports in the MMA website from 2004 to 2019 were reviewed. The number of ICSRs received per year and the number of ADRs reported in each ICSRs were identified. ADRs were grouped according to seriousness, system organ classification and patient age.

2.3 Organisation of three focus groups with healthcare professionals from different settings

Three focus groups were organised between HCPs from different settings. The first focus group included HCPs from a clinical setting and included 1 medical doctor, 1 pharmacist and 1 nurse. The second focus group included 3 pharmacists from academia and the third focus group included 3 pharmacists from the regulatory setting. The focus groups helped gather information to be included in the questionnaires and material to be used for the educational seminars.

2.4 Assessment of knowledge, attitude, practice, barriers, and need for more education of healthcare professionals on Adverse Drug Reaction reporting using a questionnaire

The knowledge, attitude, practice, barriers and need for more education of HCPs about ADR reporting were assessed using a self-administered questionnaire.

2.4.1 Development of questionnaire

Following a literature review, an anonymous self-administered questionnaire was developed. The questionnaire highlighted topics such as knowledge (Alshammari et al; 2015; Panja et al, 2015; Bhagavathula et al, 2016; Ali et al, 2018; Adisa et al, 2019; Haines et al, 2020), attitude (Mendes Marques et al, 2016; Mulatu and Worku, 2017;

AlShammari and Almoslem, 2018; Nisa et al, 2018; Adisa et al, 2019; Kassa Alemu and Biru, 2019; Hussain et al, 2021), practice (Mulatu and Worku, 2017; Laven et al, 2018; Seid et al, 2018; Al Rabayah et al, 2019; Haines et al, 2020; Hussain et al, 2021) and barriers (Wilbur, 2013; Cheema et al, 2017; Hussain et al, 2018; Li et al, 2018; Hughes and Weiss, 2019) towards ADR reporting and need for more education on PhV and ADR reporting (Biagi et al, 2013; Cheema et al, 2017; Lemay et al, 2018; Al Rabayah et al, 2019; Salehi et al, 2021). The online version of the questionnaire was created using Google Forms.

2.4.2 Validation of questionnaire

A panel of 7 members including 3 pharmacists (1 pharmacist in academia, 1 hospital pharmacist, 1 pharmacist practising in regulatory affairs), 2 nurses (2 Senior Nursing Managers at Rehabilitation Hospital) and 2 medical doctors (1 Higher Specialist Trainee in Geriatrics, 1 Specialist in Family Medicine) were recruited by convenience sampling to validate the developed questionnaire. To validate the questionnaire, the members of the panel were asked to rate each question for relevance and clarity on a Likert-Scale of 1 to 5 (5 being the highest) using a validation tool. For each question, the members of the panel were asked to indicate comments in the appropriate section. The validation tool also included a section to rate the layout of the questionnaire on a Likert-Scale of 1 to 5.

For each question, a mean rating score out of 5 was calculated. When recommended by the members of the panel, the questions were revised and rephrased. The questionnaire was rendered valid after one round validation, since all questions received a mean rating score of 4 or higher (Validation tool in Appendix 1).

The questionnaire after validation consisted of 6 sections; with a total of 29 questions (Table 2.1).

Table 2.1 Description of questionnaire assessing knowledge, attitude, practice, barriers and need for more education

Section	Questions	Description
1: Participant demographics	1-6	Gender, age, profession, area of specialisation, area of practice, years of practice
2: Knowledge	7-16	General understanding of PhV, knowledge about what type of ADR has to be report, who can report an ADR, how an ADR can be reported, the minimum criteria required for the validity of an ADR report, how an ADR reporting form should be filled in, where an ADR reporting form should to be sent, how the MMA manages the form and the impact of ADR reporting
3: Attitude	17-21	Importance of ADR reporting for medicinal products safety and patient care, ADR reporting as part of HCPs duties, remuneration, single ADR reporting, causal relationship medicinal product-ADR
4: Practice	22-23	Frequency of encountered cases of patients who experienced an ADR and frequency of reporting ADRs
5: Barriers	24	What stops an HCP from reporting an ADR
6: Education and Training	25-26	Competence and training about ADR reporting
	27a, b, c, d	Modality of acquiring updates on ADR reporting, PhV topics, day and time of the week, length

2.4.3 Determination of sample size

The Maltese Pharmacy Council reported 1292[15] pharmacists registered, the Maltese Medical Council reported 2,219[16] medical doctors and 322[16] dental practitioners registered and the Nurses and Midwives Association reported 7017[17] nurses registered.

A minimum total sample size of 372 pharmacists, medical doctors, dentists and nurses was considered representative, using a 95% confidence interval and 5% margin of error.

2.4.4 Ethics approval and dissemination of questionnaire

An approval from the Faculty of Medicine and Surgery Research Ethics Committee was obtained (Appendix 2) and the final version of the questionnaire (Appendix 3) was disseminated to pharmacists, medical doctors, dentists and nurses practising in different areas.

The questionnaire was disseminated: a) online via the social media group 'Maltese pharmacists and pharmacy students' (n=902); b) online via the mailing list of the Pharmacy Council (n=1242), of the Nurses and Midwives working within the Public Sector (n=3358), of the Malta College of Family Doctors (n=297), of the Dental Association (n=207) and of the Ministry for Health; c) personally by the researcher visiting community pharmacies (n=69). The questionnaire was disseminated between the 9th of November 2020 and the 15th of February 2021 (3 months and a half).

[15]Pharmacy Council Malta Annual Report 2020 - obtained by personal correspondence from a Pharmacy Council member. [accessed 2020 Nov 26]

[16]Medical Council of Malta. Medical Council Malta Annual Report 2018 [Internet]. Medical Council of Malta; 2018 [cited 2020 Nov 26]. Available from: https://deputyprimeminister.gov.mt/en/regcounc/medicalcouncil/Documents/AnnualReport2018.pdf

[17] Nurses and Midwives Council Malta Annual Report 2020 - obtained by personal correspondence from a Pharmacy Council member. [accessed 2020 Nov 10]

2.5 Development, validation, dissemination and evaluation of educational material on Adverse Drug Reaction reporting

Two educational webinars were developed, validated and disseminated to pharmacists, medical doctors, dentists and nurses with the aim to increase the quantity and quality of ADR reports and improve participation of HCPs in PhV activities. The educational webinars were evaluated with an evaluation form.

2.5.1 Development of educational webinars and evaluation form

Two educational webinars *"Pharmacovigilance in the time of a pandemic crisis: Adverse Drug Reaction reporting"* and *"Pharmacovigilance in the time of a pandemic crisis: Adverse Drug Reaction reporting – Part 2: Outcomes"* were developed using Microsoft PowerPoint® presentation as a result of need for more education pointed out by HCPs in the questionnaire.

The topics chosen to be discussed in the first educational webinar included: i) Background on ADRs, ii) ADR reporting system, and iii) Case studies. The topics chosen to be discussed in the second educational webinar included: i) COVID-19 vaccination - current situation, ii) Case studies, and iii) Outcomes of ADR reports and iv) Recognising ADRs in practice (Table 2.2.).

Table 2.2 Topics discussed during the educational webinars

1st Educational Webinar	Background	- Importance of ADRs and statistics - Definition of ADR and serious ADR - Underreporting and statistics - Barriers of HCPs towards ADR reporting from questionnaire/need for more education - The importance of ADR reporting and PhV - Spontaneous reporting of Covid-19 vaccination in Malta
	ADR reporting system	- General information - The Maltese ADR reporting form - Where to find it, what to report, how to fill it in, where to send it
	Case studies	- Covid-19 vaccine Pfizer-Biontech - Metformin 500mg
2nd Educational Webinar	Covid-19 vaccination-current situation	- Overview of ADR reports in Malta for Pfizer-Biontech, Astrazeneca, Moderna Covid-19 vaccines
	Case studies	- Covid-19 vaccine Pfizer-Biontech - Covid-19 vaccine Astrazeneca - Covid-19 vaccine Moderna
	Outcomes of ADR reports	- How the MMA process incoming ADRs - Safety Circulars, RMMs, DHPCs with examples
	Recognising ADRs in practice	- Key points - Outpatient and Inpatient examples - The Safety Representative: roles and tools

An evaluation form was developed to be disseminated to pharmacists, medical doctors, dentists and nurses to evaluate the educational webinars.

2.5.2 Validation of educational webinars and evaluation form

The two educational webinars and evaluation form were validated by a panel of 7 members. The members of the panel included: 4 pharmacists (2 pharmacists in academia, 2 pharmacist practising in regulatory affairs), 2 nurses (2 Senior Nursing Managers at Rehabilitation Hospital) and 1 medical doctor (1 Higher Specialist Trainee in Geriatrics). The educational webinars and the evaluation form were modified following suggestions by the members of the panel.

2.5.3 Dissemination of an invitation to attend two educational webinars

An invitation letter to attend to educational webinars was disseminated a) online via the social media group 'Maltese pharmacists and pharmacy students' (n=902); b) online via the mailing list of the Pharmacy Council (n=1242), of the Nurses and Midwives working within the Public Sector (n=3358), of the Malta College of Family Doctors (n=297), of the Dental Association (n=207) and of the Ministry for Health (Appendix 4).

2.5.4 Dissemination of educational webinars and evaluation form

The two educational webinars approved by the validation panel (Appendix 5) were disseminated via two live online webinars through the Zoom platform one on the 22nd of February 2021 (N=132 participants) and the second one on the 15th of March 2021 (N=90 participants).

An evaluation form (Appendix 6) was sent via email to the participants of the 1st and 2nd educational webinar (N= 132 and N=90 respectively).

2.6 Statistical analysis of questionnaire and evaluation form

Data of questionnaire and evaluation form were analysed using IBM SPSS statistics® 26 software. Descriptive statistics, including frequencies and percentages, were applied questions regarding participants demographics, practice of HCPs towards ADR reporting, barriers of HCPs towards ADR reporting, need for more education and training, preferred method of acquiring information on ADR reporting and preferred topics.

The Friedman test is used to compare mean scores of related aspects. The Friedman test was used for the questionnaire to compare mean knowledge scores ranging from 0 to 5 between 10 related T/F questions on ADR reporting (questions 7-16) and 5 related questions assessing the attitude of HCPs towards ADR reporting on a Likert scale of 1 to 5 (questions 17-21). The null hypothesis specifies that the mean scores vary marginally between the aspects and is accepted if the p-value is larger than 0.05 level of significance. The alternative hypothesis specifies that the mean scores vary significantly between the aspects and is accepted if the p-value is less than 0.05 criteria.

The One-Way ANOVA test is used to compare mean scores of two or more independent groups. The One-Way ANOVA test was used for the questionnaire to compare mean knowledge scores for a single question related to ADR reporting (question 7-16), or the overall mean knowledge scores, or the mean attitude scores for a single statement related to ADR reporting (question 17-21), or the mean scores for a single statement related to need for more education on ADR reporting (question 25-26) and other independent groups clustered profession and years of practice (question 3 and 6 respectively). The One-Way ANOVA test was used for the evaluation form to compare mean scores related to statements evaluating the two educational webinars (question 6-14) and profession and years of practice (question 3 and 5 respectively). The null hypothesis specifies that means are the same for the different professions or the different years of practice groups and is

accepted if the p-value exceeds the 0.05 level of significance. The alternative hypothesis specifies that means vary significantly between the different professions or the different years of practice groups and is accepted if the p-value is less than the 0.05 criterion.

The Kruskal-Wallis test is used to compare two or more independent variables. The Kruskal-Wallis test was used in the questionnaire to compare mean knowledge scores for a single question related to ADR reporting (question 7-16), or the overall mean knowledge scores, or the mean attitude scores for a single statement related to ADR reporting (question 17-21), or the mean scores for a single statement related to need for more education on ADR reporting (question 25-26) and other independent groups clustered profession and years of practice (question 3 and 6 respectively). The Kruskal-Wallis test was used for the evaluation form to compare mean scores related to statements evaluating the two educational webinars (question 6-14) and profession and years of practice (question 3 and 5 respectively). The null hypothesis specifies that the mean rating scores provided varies marginally between the groups and is accepted if the p-value exceeds the 0.05 level of significance. The alternative hypothesis specifies that the mean knowledge scores provided varies significantly between the groups and is accepted if the p-value is less than 0.05 criteria.

2.7 Dissemination of findings

An article titled “Pharmacovigilance in the time of a pandemic crisis – Adverse Drug Reaction reporting” was prepared to be submitted to the *Pharmacy Education* journal.

Chapter 3

Results

3.1 Results from the review of Individual Case Safety Reports

Between the years 2004 and 2019, 2201 ICSRs were received by the MMA. The number of ICSRs sharply increased from 2007 and 2010, and from 2016 and 2018. The highest number of ICSRs (n=223) received by the MMA was registered in 2018 (Figure 3.1).

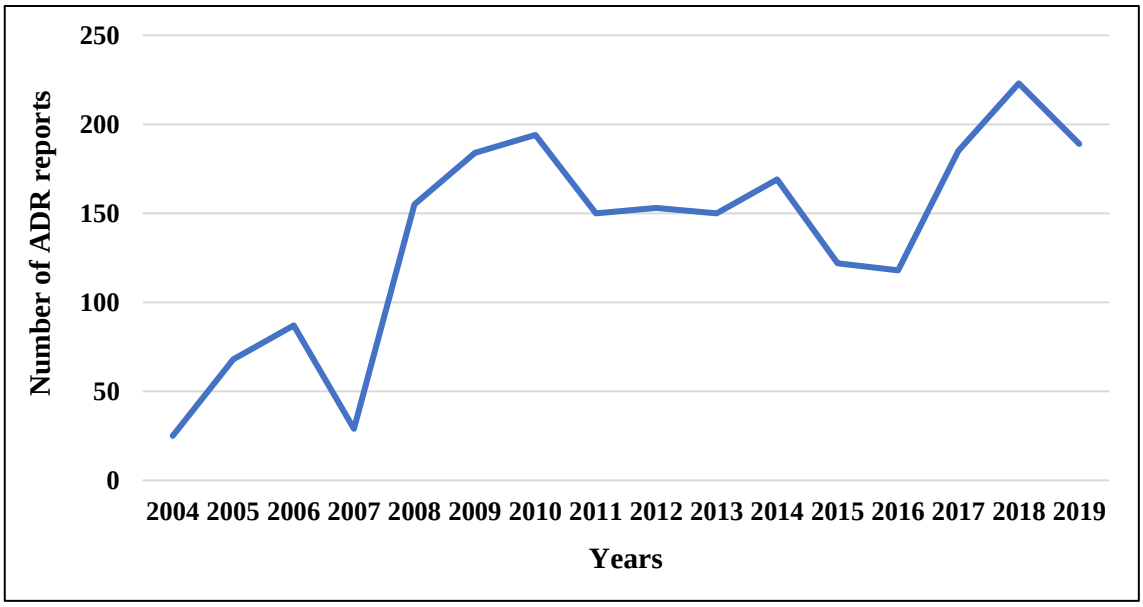

Figure 3.1 Number of ADR reports received from 2004 till 2019 (N=2201)

The mean number of ADRs reported per ICSR was 418.57±174.75. The mean percentage of serious ICSRs was 70.0%±0.25. The most frequent conditions reported, according to system organ class classification, were general disorders and administration site conditions. The table below reports the most common age group of the patients involved with an ADR (Table 3.1).

Table 3.1 Number of ADR reports received from 2004 till 2019 (N=2201)

Year	Number of ICSR	Number of ADRs reported	% Serious ADRs		Most frequent system organ class	Most common age group (years)
			n	%		
2004	25	N/A	N/A		N/A	N/A
2005	68	98	40	41	Skin disorders	40-64
2006	87	304	118	39	General disorders and skin disorders	40-64
2007	29	N/A	N/A		N/A	N/A
2008	155	634	172	27.1	N/A	18-64
2009	184	427	369	86.4	General disorders and administration site conditions	18-64
2010	194	403	354	87.9	General disorders and administration site conditions	18-64
2011	150	273	244	89.3	General disorders and administration site conditions	18-64
2012	153	300	276	92.2	Gastrointestinal disorders	12-64
2013	150	349	323	92.7	General disorders and administration site conditions	20-64
2014	169	741	649	87.6	Infections and infestations	20-64
2015	122	615	585	95.1	General disorders and administration site conditions	20-64
2016	118	613	462	75.4	General disorders and administration site conditions	18-64
2017	185	344	258	75.0	General disorders and administration site conditions	18-64
2018	223	431	198	46.0	General disorders and administration site conditions	18-64
2019	189	328	134	41.0	General disorders and administration site conditions	18-64

3.2 Results from the focus groups

The focus groups helped identify questions to be included in the first questionnaire and information to be presented during the educational webinars. During the focus groups the following suggestions were put forward by the members of the expert panels: to include questions regarding the ADR reporting form (such as where to find it, where to send it, how to fill it in, who can report), list of barriers encountered when reporting an ADR and outcomes of ADR reporting for the questionnaire.

The expert panel also suggested that during the educational webinar, an ADR reporting form should have been provided to the HCPs to explain them how to fill it in. HCPs should have been explained what the MMA does with the ADR reports and provided with actual data on activities in ADR reporting.

3.3 Results of questionnaire used to assess knowledge, attitude, practice, barriers and need for more education on Adverse Drug Reaction reporting

In Section 3.3 results of the questionnaire assessing knowledge, attitude, practice, barriers and need for more education of HCPs on ADR reporting are described.

3.3.1 Participant demographics

The questionnaire was completed by 374 participants; 89.3% (n=334) completed the questionnaire online and 10.7% of the completed questionnaires (n=40) were collected personally by the researcher. The majority of respondents (44.7%, n=167) were pharmacists (Figure 3.2).

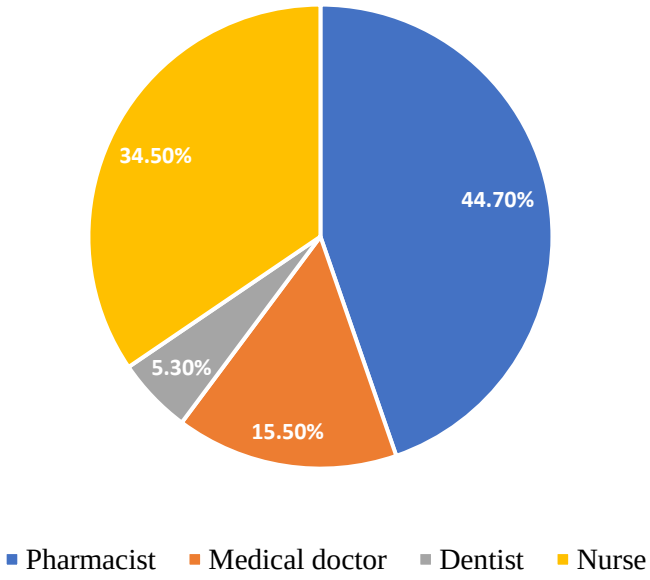

Figure 3.2 Profession (N=374)

Sixty five percent (n=108) and 69.8% (n=90) of pharmacists and nurses respectively were female; for medical doctors 62.1% (n=36) were male; while for dentists, an almost equal distribution between genders was observed (male 55%, n=11; female 45%, n=9).

The highest number of pharmacists and nurses was in the 21-35 years age-group (pharmacists 44.91%, n=75; nurses 33.55%, n=42); the highest number of medical

doctors was in the 56-69 years age-group (37.93%, n=22); while the highest number of dentists was in the 36-45 years age-group (35%, n=7) (Table 3.2).

Table 3.2 HCPs' distribution by age group (N=374)

	Pharmacists (n=167)		**Medical Doctors (n=58)**		**Dentists (n=20)**		**Nurses (n=129)**	
Age group	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
21-35 years	**75**	**44.9**	9	15.6	5	25	**42**	**32.5**
36-45 years	41	24.5	12	20.7	**7**	**35**	23	17.9
46-55 years	39	23.4	14	24.1	3	15	40	31
56-69 years	12	7.2	**22**	**37.9**	4	20	24	18.6
>70 years	0	0	1	1.7	1	5	0	0

The highest number of pharmacists and the majority of medical doctors and nurses had more than 20 years of practice (pharmacists 44.91%, n=51; medical doctors 53.44%, n=31; nurses 50.38%, n=65); while the highest number of dentists had between 11 and 20 years of practice (40%, n=8) (Table 3.3).

Table 3.3 HCPs' distribution by years of practice (N=374)

	Pharmacists (n=167)		**Medical Doctors (n=58)**		**Dentists (n=20)**		**Nurses (n=129)**	
Years of practice	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
< 2 years	23	13.7	4	6.9	0	0	13	10.1
2-5 years	23	13.7	3	5.2	5	25	20	15.5
6-10 years	31	18.6	3	5.2	0	0	14	10.9
11-20 years	39	23.4	17	29.3	**8**	**40**	17	13.1
>20 years	**51**	**30.5**	**31**	**53.4**	7	35	**65**	**50.4**

Most of the pharmacists who completed the questionnaire practiced in the community pharmacy setting (46.7%, n=91), most of the doctors and the majority of nurses practiced in the hospital setting (34.1%, n=29; 70.5%, n=105); while the majority of dentists practiced in a private clinic (70.4%, n=19) (Table 3.4).

Table 3.4 HCPs' distribution by area of practice (N=374)

	Pharmacists (n=167)		**Medical Doctors (n=58)**		**Dentists (n=20)**		**Nurses (n=129)**	
Area of practice	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
Community	**91**	**46.7**	12	14.1	0	0	1	0.7
Academia	12	6.1	6	7.1	4	14.8	1	0.7
Hospital	25	12.8	**29**	**34.1**	2	7.4	**105**	**70.5**
Industry	38	19.5	0	0	0	0	0	
Regulatory	28	14.4	0	0	0	0	3	2.0
Nursing Home	0	0	0	0	0	0	27	18.1
Health Centre	1	0.5	10	11.8	2	7.4	9	6.0
Private Clinic	0	0	28	32.9	**19**	**70.4**	3	2.0

3.3.2 Knowledge of healthcare professionals on Adverse Drug Reaction reporting

HCPs had a good knowledge on PhV and ADR reporting (mean knowledge score 42.02/50±3.90).

Pharmacists (43.66/50) were significantly more knowledgeable on ADR reporting; while nurses (39.41) were significantly less knowledgeable (p<0.001) (Table 3.5).

Table 3.5 HCPs' mean overall knowledge scores on ADR reporting by profession (N=374)

Profession	Mean ± SD	p- value
Pharmacists (n=167)	43.66 ± 3.21	**<0.001***
Medical Doctors (n=58)	43.24 ± 2.36	
Dentists (n=20)	41.60 ± 1.93	
Nurses (n=129)	39.41 ± 4.11	

Healthcare professionals with 11 to 20 years of practice (43.25/50) were found to be more knowledgeable about ADR reporting than the other groups of HCPS (p=0.010) (Table 3.6).

Table 3.6 HCPs' mean overall knowledge scores on ADR reporting by years of practice (N=374)

Years of practice	Mean ± SD	p- value
< 2 years (n=40)	40.73 ± 4.49	**0.010***
2-5 years (n=51)	42.35 ± 4.07	
6-10 years (n=48)	42.06 ± 3.95	
11-20 years (n=81)	43.25 ± 2.25	
> 20 years (n=154)	41.58 ± 4.20	

The mean knowledge score for "who can report an ADR" (4.67) is the largest, indicating highest knowledge of HCPs on this question. The mean rating score for "How should an ADR reporting form be filled in?" (3.02) is the lowest, indicating least knowledge. The p-value of the Friedman test (approximately 0) is less than 0.05 level of significance (Table 3.7).

Table 3.7 HCPs' mean knowledge scores on ADR reporting (N=374)

Statement	N	Mean	SD
What is the scope of Pharmacovigilance?	374	4.20	.729
Which of these statements about ADRs is true?	374	4.33	.780
What type of ADRs should be reported by HCPs?	374	4.42	.883
Who can report an ADR?	374	**4.67**	**.681**
How can ADRs be reported?	374	3.91	.821
What needs to be included in an ADR report?	374	4.41	.699
How should an ADR reporting form be filled in?	374	**3.02**	**.696**
Where should the ADR reporting form be sent?	374	4.12	.786
How does the MMA manage the ADR reports?	374	4.32	.894
What is the impact of ADR reporting?	374	4.61	.796

$X^2(9) = 975.766$, $p < 0.001$

Pharmacists (4.40) and medical doctors (4.40) were significantly more knowledgeable than dentists (4.15) and nurses (3.87) on what was the scope of PhV ($p<0.001$). Pharmacists (4.22) were significantly more knowledgeable than medical doctors (3.97), dentists (3.65) and nurses (3.53) about how ADRs could be reported ($p<0.001$).

Nurses were less knowledgeable than pharmacists, medical doctors and dentists on how to fill in an ADR reporting form, where the ADR reporting for should be sent and how the MMA manages the ADR reports ($p<0.005$) (Table 3.8).

Table 3.8 HCPs' mean knowledge scores on ADR reporting by profession (N=374)

Statement	Profession	Mean ± SD	p-value
What is the scope of Pharmacovigilance?	Pharmacist (n=167)	4.40 ± 0.68	**<0.001***
	Medical Doctor (n=58)	4.40 ± 0.72	
	Dentist (n=20)	4.15 ± 0.59	
	Nurse (n=129)	3.87 ± 0.70	
Which of these statements about ADRs is true?	Pharmacist (n=167)	4.44 ± 0.72	**0.003***
	Medical Doctor (n=58)	4.48 ± 0.63	
	Dentist (n=20)	4.25 ± 0.64	
	Nurse (n=129)	4.13 ± 0.90	
What type of ADRs should be reported by HCPs?	Pharmacist (n=167)	4.45 ± 0.84	0.627
	Medical Doctor (n=58)	4.55 ± 0.75	
	Dentist (n=20)	4.40 ± 0.88	
	Nurse (n=129)	4.33 ± 0.99	
Who can report an ADR?	Pharmacist (n=167)	4.71 ± 0.66	0.428
	Medical Doctor (n=58)	4.62 ± 0.70	
	Dentist (n=20)	4.65 ± 0.49	
	Nurse (n=129)	4.63 ± 0.73	
How can ADRs be reported?	Pharmacist (n=167)	4.22 ± 0.76	**<0.001***
	Medical Doctor (n=58)	3.97 ± 0.67	
	Dentist (n=20)	3.65 ± 0.87	
	Nurse (n=129)	3.53 ± 0.78	
What needs to be included in an ADR report?	Pharmacist (n=167)	4.59 ± 0.59	**<0.001***
	Medical Doctor (n=58)	4.41 ± 0.79	
	Dentist (n=20)	4.30 ± 0.57	
	Nurse (n=129)	4.18 ± 0.73	
How should an ADR reporting form be filled in?	Pharmacist (n=167)	3.13 ± 0.76	**0.002***
	Medical Doctor (n=58)	3.10 ± 0.61	
	Dentist (n=20)	3.00 ± 0.56	
	Nurse (n=129)	2.84 ± 0.63	
Where should the ADR reporting form be sent?	Pharmacist (n=167)	4.29 ± 0.69	**0.001***
	Medical Doctor (n=58)	4.17 ± 0.73	
	Dentist (n=20)	4.15 ± 0.74	
	Nurse (n=129)	3.88 ± 0.87	
How does the MMA manage the ADR reports?	Pharmacist (n=167)	4.56 ± 0.81	**<0.001***
	Medical Doctor (n=58)	4.66 ± 0.55	
	Dentist (n=20)	4.30 ± 0.57	
	Nurse (n=129)	3.88 ± 0.98	
What is the impact of ADR reporting?	Pharmacist (n=167)	4.87 ± 0.44	**<0.001***
	Medical Doctor (n=58)	4.88 ± 0.38	
	Dentist (n=20)	4.75 ± 0.44	
	Nurse (n=129)	4.14 ± 1.07	

*statistically significant results $p<0.05$

HCPs that practiced between 11 and 20 years were found to be more knowledgeable about statements regarding ADRs ($p<0.001$), about what information to include in an ADR report ($p=0.004$) and about how the MMA manages the ADR reports that receives ($p=0.022$) (Table 3.9).

Table 3.9 HCPs' mean knowledge scores on ADR reporting by years of practice (N=374)

Statement	Years of practice	Mean ± SD	p-value
What is the scope of Pharmacovigilance?	< 2 years (n=40)	3.93 ± 0.69	0.097
	2-5 years (n=51)	4.20 ± 0.75	
	6-10 years (n=48)	4.25 ± 0.79	
	11-20 years (n=81)	4.21 ± 0.74	
	> 20 years (n=154)	4.25 ± 0.70	
Which of these statements about ADRs is true?	< 2 years (n=40)	4.28 ± 0.85	**<0.001***
	2-5 years (n=51)	4.39 ± 0.63	
	6-10 years (n=48)	4.50 ± 0.68	
	11-20 years (n=81)	4.60 ± 0.54	
	> 20 years (n=154)	4.13 ± 0.88	
What type of ADRs should be reported by HCPs?	< 2 years (n=40)	4.35 ± 0.92	0.699
	2-5 years (n=51)	4.57 ± 0.73	
	6-10 years (n=48)	4.50 ± 0.82	
	11-20 years (n=81)	4.41 ± 0.833	
	> 20 years (n=154)	4.37 ± 0.96	
Who can report an ADR?	< 2 years (n=40)	4.60 ± 0.67	0.139
	2-5 years (n=51)	4.82 ± 0.55	
	6-10 years (n=48)	4.60 ± 0.84	
	11-20 years (n=81)	4.77 ± 0.48	
	> 20 years (n=154)	4.60 ± 0.75	
How can ADRs be reported?	< 2 years (n=40)	3.88 ± 0.85	0.897
	2-5 years (n=51)	3.88 ± 0.84	
	6-10 years (n=48)	3.92 ± 0.99	
	11-20 years (n=81)	3.99 ± 0.73	
	> 20 years (n=154)	3.90 ± 0.80	
What needs to be included in an ADR report?	< 2 years (n=40)	4.20 ± 0.69	**0.004***
	2-5 years (n=51)	4.39 ± 0.72	
	6-10 years (n=48)	4.21 ± 0.74	
	11-20 years (n=81)	4.62 ± 0.56	
	> 20 years (n=154)	4.42 ± 0.72	
How should an ADR reporting form be filled in?	< 2 years (n=40)	3.00 ± 0.88	0.580
	2-5 years (n=51)	2.94 ± 0.88	
	6-10 years (n=48)	2.92 ± 0.54	
	11-20 years (n=81)	3.12 ± 0.64	
	> 20 years (n=154)	3.03 ± 0.65	
Where should the ADR reporting form be sent?	< 2 years (n=40)	4.03 ± 0.86	0.118
	2-5 years (n=51)	4.27 ± 0.83	
	6-10 years (n=48)	4.23 ± 0.88	
	11-20 years (n=81)	4.19 ± 0.70	
	> 20 years (n=154)	4.03 ± 0.76	
How does the MMA manage the ADR reports?	< 2 years (n=40)	4.00 ± 1.04	**0.022***
	2-5 years (n=51)	4.24 ± 0.95	
	6-10 years (n=48)	4.23 ± 0.90	
	11-20 years (n=81)	4.53 ± 0.78	
	> 20 years (n=154)	4.36 ± 0.87	
What is the impact of ADR reporting?	< 2 years (n=40)	4.47 ± 0.96	0.076
	2-5 years (n=51)	4.65 ± 0.80	
	6-10 years (n=48)	4.71 ± 0.77	
	11-20 years (n=81)	4.81 ± 0.42	
	> 20 years (n=154)	4.51 ± 0.89	

*statistically significant results $p<0.05$

3.3.3 Attitude of healthcare professionals towards Adverse Drug Reaction reporting

HCPs strongly agreed that reporting an ADR was important for medicinal products' safety and patient care (4.87) and that ADR reporting was part of their duty as HCPs (4.81). HCPs disagreed with the statement "the single ADR I report does not contribute to the safety of that medicinal product" (2.00) and with any kind of remuneration to encourage them to report an ADR ($p<0.001$) (Table 3.10).

Table 3.10 Mean rating attitude score of HCPs towards ADR reporting (N=374)

Statement	N	Mean ± SD
Reporting is important for medicinal products safety and patient care	374	4.87 ± 0.56
ADR reporting is part of my duty as a HCP	374	4.81 ± 0.55
The single ADR I report does not contribute to the safety of that medicinal product	374	2.00 ± 1.21
Before reporting any ADR, I want to be sure that the ADR is caused by the medicinal product	374	3.64 ± 1.34
Remuneration for ADR reporting could encourage me to report	374	2.25 ± 1.37

$X^2(4) = 1010.248$, $p < 0.001$

Dentists (4.00) and nurses (3.94) agreed more than pharmacists (3.35) and medical doctors (3.71) that they wanted to confirm that it was the medical product causing the ADR before reporting the event ($p=0.002$). Pharmacists (2.08) disagreed more than medical doctors (2.24), dentists (2.15) and nurses (2.52) that any kind of remuneration could encourage them to report an ADR ($p=0.041$) (Table 3.11).

Table 3.11 Mean rating attitude score of HCPs towards ADR reporting by profession (N=374)

Statement	Profession	Mean ± SD	p-value
Reporting is important for medicinal products safety and patient care	Pharmacist (n=167)	4.89 ± 0.42	0.640
	Medical Doctor (n=58)	4.86 ± 0.60	
	Dentist (n=20)	4.90 ± 0.31	
	Nurse (n=129)	4.85 ± 0.71	
ADR reporting is part of my duty as a HCP	Pharmacist (n=167)	4.83 ± 0.49	0.960
	Medical Doctor (n=58)	4.84 ± 0.45	
	Dentist (n=20)	4.75 ± 0.64	
	Nurse (n=129)	4.78 ± 0.65	
The single ADR I report does not contribute to the safety of that medicinal product	Pharmacist (n=167)	1.87 ± 1.15	0.166
	Medical Doctor (n=58)	1.95 ± 1.15	
	Dentist (n=20)	1.95 ± 1.19	
	Nurse (n=129)	2.20 ± 1.29	
Before reporting any ADR, I want to be sure that the ADR is caused by the medicinal product	Pharmacist (n=167)	3.35 ± 1.44	**0.002***
	Medical Doctor (n=58)	3.71 ± 1.14	
	Dentist (n=20)	4.00 ± 1.08	
	Nurse (n=129)	3.94 ± 1.27	
Remuneration for ADR reporting could encourage me to report	Pharmacist (n=167)	2.08 ± 1.32	**0.041***
	Medical Doctor (n=58)	2.24 ± 1.37	
	Dentist (n=20)	2.15 ± 1.50	
	Nurse (n=129)	2.52 ± 1.40	

HCPs with less than 2 years of practice (4.18) agreed more than the other groups that they wanted to confirm that it was the medical product causing the ADR before reporting the event (p=0.014). HCPs with 11 to 20 years of practice strongly disagreed more than the other groups that any kind of remuneration could encourage them to report an ADR (p=0.003) (Table 3.12).

Table 3.12 Mean rating attitude score of HCPs towards ADR reporting by years of practice (N=374)

Statement	Years of practice	Mean ± SD	p-value
Reporting is important for medicinal products safety and patient care	< 2 years (n=40)	4.93 ± 0.27	0.922
	2-5 years (n=51)	4.86 ± 0.60	
	6-10 years (n=48)	4.81 ± 0.67	
	11-20 years (n=81)	4.88 ± 0.51	
	> 20 years (n=154)	4.88 ± 0.59	
ADR reporting is part of my duty as a HCP	< 2 years (n=40)	4.78 ± 0.48	0.136
	2-5 years (n=51)	4.92 ± 0.27	
	6-10 years (n=48)	4.67 ± 0.75	
	11-20 years (n=81)	4.86 ± 0.44	
	> 20 years (n=154)	4.79 ± 0.61	
The single ADR I report does not contribute to the safety of that medicinal product	< 2 years (n=40)	1.83 ± 0.98	0.374
	2-5 years (n=51)	2.08 ± 1.25	
	6-10 years (n=48)	1.98 ± 1.19	
	11-20 years (n=81)	1.75 ± 0.98	
	> 20 years (n=154)	2.16 ± 1.34	
Before reporting any ADR, I want to be sure that the ADR is caused by the medicinal product	< 2 years (n=40)	4.18 ± 0.78	**0.014***
	2-5 years (n=51)	3.94 ± 1.26	
	6-10 years (n=48)	3.75 ± 1.33	
	11-20 years (n=81)	3.40 ± 1.30	
	> 20 years (n=154)	3.51 ± 1.47	
Remuneration for ADR reporting could encourage me to report	< 2 years (n=40)	2.75± 1.33	**0.003***
	2-5 years (n=51)	2.73 ± 1.49	
	6-10 years (n=48)	2.19 ± 1.42	
	11-20 years (n=81)	1.96 ± 1.20	
	> 20 years (n=154)	2.16 ± 1.37	

3.3.4 Practice of healthcare professionals towards Adverse Drug Reaction reporting

Most of the HCPs stated to have encountered an ADR yearly (37.4%, n=140), while 34.2% (n=128) have never encountered an ADR (Table 3.13).

Table 3.13 Frequency of encountering an ADR (N=374)

How often do you encounter patients experiencing ADRs?	*n*	*%*
No cases	**128**	**34.2**
Daily	8	2.1
Weekly	22	5.9
Monthly	76	20.3
Yearly	**140**	**37.4**

Most of pharmacists (33.5%, n=56) and the majority of medical doctors (53.5%, n=31) stated to have encountered ADRs yearly; while the majority of dentists (55.0%, n=11) and nurses (52.8%, n=68) have never encountered an ADR (Figure 3.3).

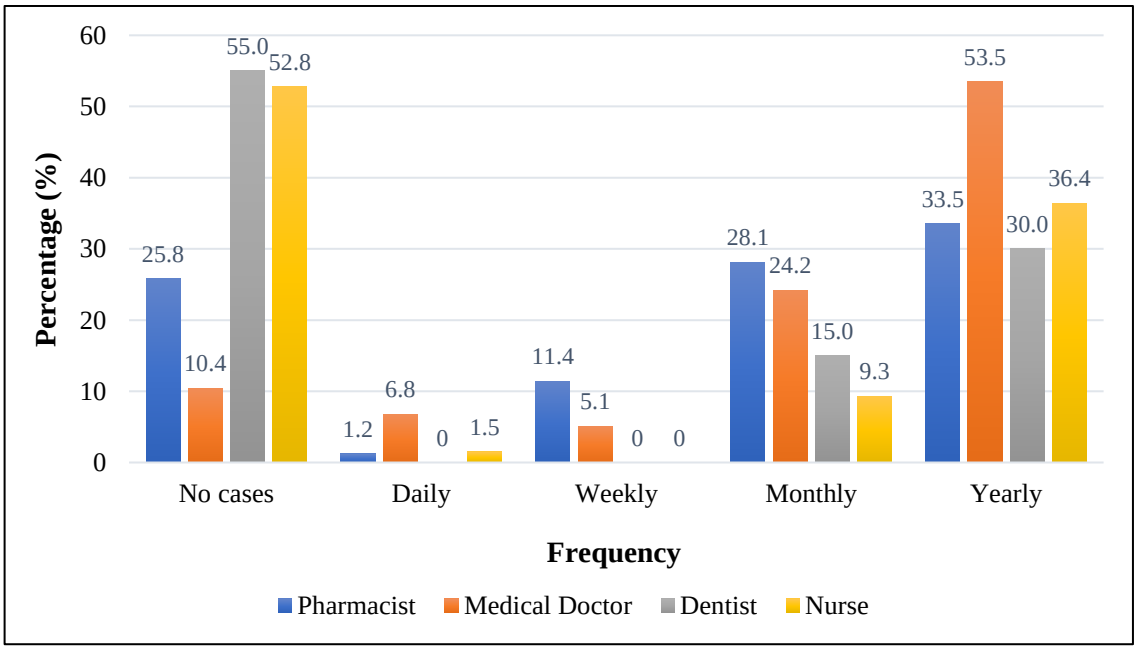

Figure 3.3 Frequency of encountering an ADR by profession (N=374)

Out of the HCPs who encountered an ADR (65.8%, n=246), 30.1% (n=74) and 23.6% (n=23.6) almost never or rarely reported the event, respectively (Table 3.14).

Table 3.14 Frequency of reporting an ADR when encountered (N=246)

How often have you reported an ADR when encountered?	*n*	*%*
Almost never	**74**	**30.1**
Rarely	**58**	**23.6**
Sometimes	37	15
Very frequently	24	9.8
Almost always	53	21.5

Out of the HCPs who encountered an ADR (65.8%, n=246), 36.3% of pharmacists (n=45) and the majority of dentists (77.8%, n=7) almost never reported the event. Most of doctors (30.8%, n=16) rarely reported the event; while most of nurses (31.2%, n=19) almost always reported the event. (Figure 3.4).

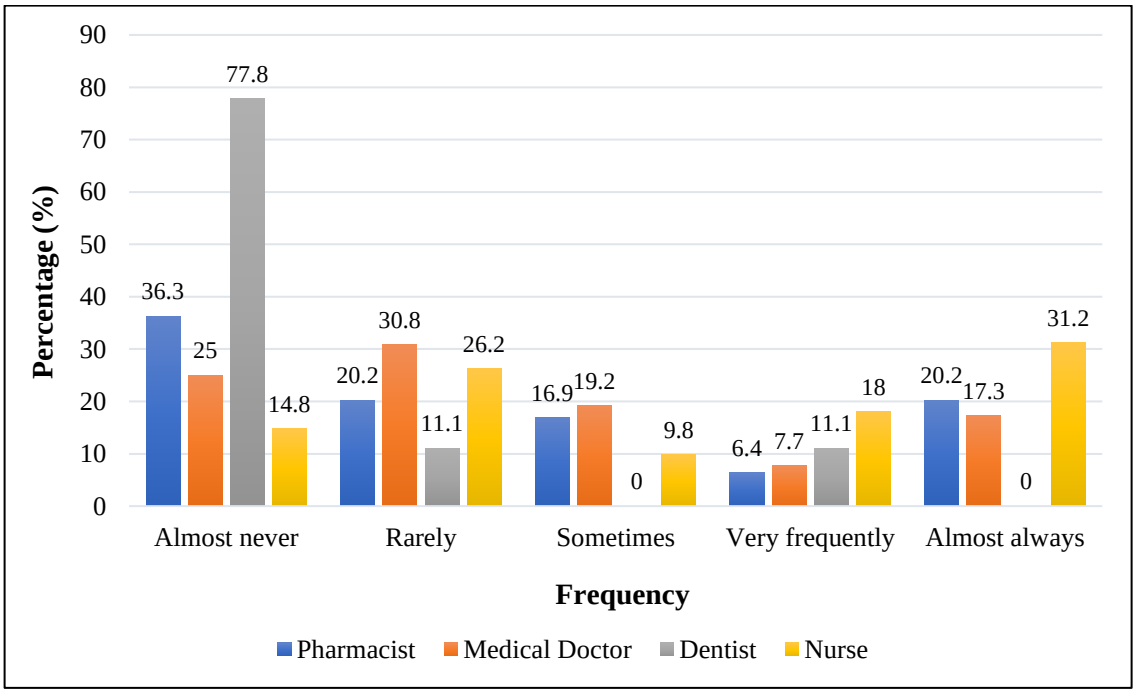

Figure 3.4 Frequency of reporting an ADR when encountered by profession (N=246)

3.3.5 Barriers of healthcare professionals towards adverse drug reaction reporting

The majority of HCPs (50%, n=187) stated that the main reason that stopped them from reporting an ADR was the difficulty to understand whether an ADR has occurred. This is followed by ADRs being already well known and documented to occur (43.9%, n=164), patients followed up by different HCPs (35.0%, n=131) and lack of time (32.4%, n=121). Other reasons for not reporting were: 'I forget' (n=11), 'Lack of patients collaboration' (n=6) and 'Not working with patients' (n=4) (Table 3.15).

Table 3.15 Barriers of HCPs towards ADR reporting (N=374)

Barrier	*n*	*% of cases*
Difficulty to understand whether an ADR has occurred or not	**187**	**50.0%**
ADR already well known and documented to occur	**164**	**43.9%**
Patient followed up by different professionals	**131**	**35.0%**
Lack of time	**121**	**32.4%**
Difficulty in accessing ADR reporting form	88	23.5%
Not knowing where to send the ADR reporting form	84	22.5%
Limited understanding of its value	59	15.8%
Concern that ADR reporting may generate extra work	50	13.4%
Not being aware that ADRs may be reported	41	11.0%
Lack of motivation	38	10.2%
Fear of consequences	29	7.8%
Other	21	5.6%

The main reason for pharmacists and medical doctors was ADRs being already well known and documented to occur (50.9%, n=85 and 56.9%, n=33 respectively), followed by difficulty to understand whether an ADR occurred (45.5%, n=76 and 53.4%, n=31 respectively) and lack of time (44.3%, n=74 and 48.3%, n=28 respectively).

The barriers listed by dentists were: ADRs being already well known and documented to occur (55%, n=11), difficulty to understand whether an ADR occurred (50%, n=10) and not knowing where to send the ADR reporting form (45%, n=9).

Barriers encountered by nurses were: difficulty to understand whether an ADR occurred (54.3%, n=70), not knowing where to send the ADR reporting form (36.4%, n=47) and difficulty in accessing the ADR reporting form (34.1%, n=44) (Table 3.16).

Table 3.16 Barriers of HCPs towards ADR reporting by profession (N=374)

	Pharmacists (n=167)		**Medical Doctors (n=58)**		**Dentists (n=20)**		**Nurses (n=129)**	
Barriers	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
Limited understanding of its value	18	10.8	6	10.3	1	5	34	26.4
Difficulty in accessing ADR reporting form	23	13.8	13	22.4	8	40	**44**	34.1
Lack of time	**74**	44.3	**28**	48.3	2	10	17	13.2
Lack of motivation	19	11.4	9	15.5	2	10	8	6.2
Fear of consequences	6	3.6	3	5.2	1	5	19	14.7
Not knowing where to send the ADR reporting form	15	9.0	13	22.4	**9**	45	**47**	36.4
Concern that ADR reporting may generate extra work	19	11.4	16	27.6	0	0	15	11.6
Difficulty to understand whether an ADR has occurred or not	**76**	45.5	**31**	53.4	**10**	50	**70**	54.3
Patient followed up by different professionals	67	40.1	21	36.2	6	30	37	28.7
ADR already well known and documented to occur	**85**	50.9	**33**	56.9	**11**	55	35	27.1
Not being aware that ADRs may be reported	10	6.0	2	3.4	3	15	26	20.2
Other	14	8.4	3	5.2	0	0	4	3.1

3.3.6 Education and training of healthcare professionals about Adverse Drug Reaction reporting

Most of HCPs agreed and strongly agreed with the statement "I believe I am competent in the area of ADR reporting (26.5%, n=99 and 11.2%, n=42 respectively) (Table 3.17).

Table 3.17 Competency on ADR reporting (N=374)

I believe I am competent in the area of ADR reporting	*n*	*%*
Strongly disagree	39	10.4
Disagree	59	15.8
Neutral	135	36.1
Agree	**99**	**26.5**
Strongly agree	**42**	**11.2**

The majority of HCPs agreed and strongly agreed with the statement "I require more education on ADR reporting (strongly agree: 40.4%, n=151; agree 31.8%, n=119) (Table 3.18).

Table 3.18 Need for more education about ADR reporting (N=374)

I require more education on ADR reporting	*n*	*%*
Strongly disagree	14	3.7
Disagree	39	10.4
Neutral	51	13.6
Agree	**119**	**31.8**
Strongly agree	**151**	**40.4**

Dentists (2.35) and nurses (2.69) significantly disagreed more than pharmacists (3.53) and medical doctors (3.19) that they were competent in the area of ADR reporting ($p<0.001$) and significantly strongly agreed that they required more education on ADR reporting (dentists 4.15; nurses 4.41) ($p<0.001$) (Table 3.19).

Table 3.19 Education and training about ADR reporting by profession (N=374)

Statement	Profession	Mean ± SD	p-value
I believe I am competent in the area of ADR reporting	Pharmacist (n=167)	3.53 ± 1.10	**<0.001***
	Medical Doctor (n=58)	3.19 ± 0.98	
	Dentist (n=20)	2.35 ± 0.88	
	Nurse (n=129)	2.69 ± 1.06	
I require more education on ADR reporting	Pharmacist (n=167)	3.60 ± 1.27	**<0.001***
	Medical Doctor (n=58)	3.84 ± 0.99	
	Dentist (n=20)	4.15 ± 0.88	
	Nurse (n=129)	4.41 ± 0.86	

*statistically significant results $p<0.05$

HCPs preferred continuing professional education seminars (65.8%, n=246) and guidelines/publications (56.4%, n=211) for acquiring more education on ADR reporting. Other suggested ways how to obtain more information on ADR reporting were: ‘emails’ (n=18) and ‘courses in undergraduate curricula’ (n=10). Ten of them (2.7%) were not interested in receiving these updates (Table 3.20).

Table 3.20 Preferred method of acquiring information on ADR reporting (N=374)

Preferred method of acquiring information on ADR reporting	*n*	*% of cases*
Continuing professional education seminars	**246**	**65.8%**
Guidelines/Publications	**211**	**56.4%**
Courses	82	21.9%
Workshops	77	20.6%
Conferences	76	20.3%
I am not interested	10	2.7%
Others	28	7.5%

The majority of pharmacists (67.1%, n=112) and nurses (71.3%, n=92) preferred continuing professional education seminars for acquiring more education on ADR reporting; while the majority of medical doctors (62.1, n=36) and dentists (65%, n=13) preferred guidelines/publications (Table 3.21).

Table 3.21 Preferred method of acquiring information on ADR reporting by profession (N=364)

	Pharmacists (n=167)		**Medical Doctors (n=58)**		**Dentists (n=20)**		**Nurses (n=129)**	
Preferred method	n	%	n	%	n	%	n	%
Continuing professional education seminars	**112**	**67.1**	31	53.4	11	55	**92**	**71.3**
Courses	33	19.8	4	6.9	4	20	41	31.8
Conferences	29	17.4	8	13.8	2	10	37	28.7
Workshops	37	22.2	9	15.5	2	10	29	22.5
Guidelines/Publications	93	55.7	**36**	**62.1**	**13**	**65**	69	53.5
I am not interested	6	3.6	3	5.2	0	0	1	0.8
Other	11	6.6	6	10.3	0	0	11	8.5

HCPs (47.0%, n=171) preferred following the selected learning activities as a combination of attending in person and following online material or only online (46.2%, n=168). The majority of pharmacists (51,5%, n=83), medical doctors (52.8%, n=29) and dentists (60%, n=12) preferred following the selected learning activities online; while the majority of nurses (54.7%, n=70) preferred following the selected learning activities as a combination of attending in person and following online material.

ADR reporting was the topic of highest preference for HCPs (86.6%, n=316). Other suggested topics were: 'Classification of ADRs' (n=3), 'Outcomes of ADR reporting' (n=2), 'Pharmacovigilance' (n=2), 'Risk-benefit evaluation and continuous monitoring' (n=2), 'Medication interactions' (n=1), 'Legislation and practical implication' (n=1), 'Innovative network' (n=1) (Table 3.22).

Table 3.22 Preferred topics (N=364)

Preferred topics	*n*	*% of cases*
ADR reporting	**316**	**86.6%**
Medication errors	279	76.4%
How ADR reporting contributes to drug safety	238	65.2%
Others	12	3.3%

'ADR reporting' was the topic of highest preference for pharmacists (84.5%, n=136), medical doctors (80%, n=44), dentists (95%, n=19) and nurses (91.4%, n=117) (Table 3.23).

Table 3.23 Preferred topics by profession (N=364)

	Pharmacists (n=161)		Medical Doctors (n=55)		Dentists (n=20)		Nurses (n=128)	
Preferred topics	n	%	n	%	n	%	n	%
ADR reporting	**136**	**84.5**	**44**	**80**	**19**	**95**	**117**	**91.4**
Medication errors	134	83.2	30	54.5	17	85	98	76.6
How ADR reporting contributes to drug safety	95	59.0	28	50.9	16	80	99	77.3
Other	9	5.6	2	3.6	0	0	1	0.8

3.4 Results of the evaluation of the educational webinars

In Section 3.4, results of the two educational webinars delivered via Zoom platform are described.

3.4.1 First educational webinar – Participants demographics

The first educational webinar was attended by 132 HCPs. The evaluation form was completed by 103 participants. Participants distribution was 63 pharmacists (female n=42; male n=21), 14 medical doctors (female n=12; male n=2), 6 dentists (female n=2; male n=4) and 20 nurses (female n=17; male n=3). The mean age for pharmacists was 36, for medical doctors 45, for dentists 54 and for nurses 49. The mean years of practice for pharmacists was 12 years, for medical doctors 19 years, for dentists 28 years and for nurses 21 years (Table 3.24).

Table 3.24 Evaluation form – Participants demographics (N=103)

	Gender		**Age (years)**	**Years of practice**
	Female (n)	*Male (n)*	*Mean ±SD*	*Mean ±SD*
Pharmacists (n=63)	42	21	36±10.01	12±9.76
Medical Doctors (n=14)	12	2	45±17.33	19±18.35
Dentists (n=6)	2	4	54±19.83	28±20.89
Nurses (n=20)	17	3	49±8.98	21±6.93

Most pharmacists who completed the evaluation form practiced in community pharmacy (n=28). The majority of nurses (n=17) and medical doctors (n=5) practiced in hospital. Most dentists practiced in Academia (n=3) (Table 3.25).

Table 3.25 Evaluation form – HCPs' distribution by area of practice (N=103)

	Pharmacists (n=63)		**Medical Doctors (n=14)**		**Dentists (n=6)**		**Nurses (n=20)**	
Area of practice	*n*	*%*	*n*	*%*	*n*	*%*	*n*	*%*
Community	**28**	**44.4**	3	21.4	0	0	2	10
Academia	7	11.1	1	7.1	3	50	1	5
Hospital	11	17.4	**5**	**35.8**	2	33.3	**17**	**85**
Industry	10	15.9	1	7.1	0	0	0	0
Regulatory	24	38.1	1	7.1	0	0	0	0
Nursing Home	0	0	1	7.1	1	16.7	0	0
Health Centre	0	0	3	21.4	0	0	1	5
Private Clinic	1	1.6	2	14.3	2	**33.3**	0	0

3.4.2 Evaluation of first educational webinar

With regards to the educational content, pharmacists, medical doctors, dentists and nurses agreed that the sequence of material provided was appropriate and the information was clearly presented. Both medical doctors and nurses strongly agreed with a significantly higher mean rating score that the information in the educational webinar was comprehensive (medical doctors 4.86, nurses 4.90; p=0.003). Medical doctors significantly strongly agreed that the educational webinar was relevant for their practice (4.71; p=0.014). Nurses significantly strongly agreed more than pharmacists, medical doctors and dentists that the educational webinar made them more aware of the importance of ADR reporting (4.85; p=0.039) and that it helped them to overcome barriers toward ADR reporting (4.70; p=0.047). Both pharmacists and medical doctors significantly agreed more than dentists and nurses that following the educational webinar they are more confident with ADR reporting (pharmacists 4.38, medical doctors 4.50; p=0.036). Medical doctors significantly strongly agreed more than pharmacists, dentists and nurses that the educational webinar met their expectations (4.71; p=0.039) (table 3.26).

Table 3.26 Evaluation of first educational webinar (N=103)

Statement	Profession	Mean ± SD	p-value
The sequence of material was appropriate	Pharmacist (n=63)	4.68±0.47	0.111
	Medical Doctor (n=14)	4.71±0.47	
	Dentist (n=6)	4.33±0.51	
	Nurse (n=20)	4.85±0.37	
Information in the educational webinar was clearly presented	Pharmacist (n=63)	4.76±0.43	0.168
	Medical Doctor (n=14)	4.86±0.36	
	Dentist (n=6)	4.50±0.55	
	Nurse (n=20)	4.90±0.30	
Information in the educational webinar was comprehensive	Pharmacist (n=63)	4.67±0.54	**0.003***
	Medical Doctor (n=14)	4.86±0.36	
	Dentist (n=6)	3.50±1.50	
	Nurse (n=20)	4.95±0.22	
The educational webinar was relevant for my practice	Pharmacist (n=63)	4.56±0.64	**0.014***
	Medical Doctor (n=14)	4.71±0.47	
	Dentist (n=6)	3.50±0.83	
	Nurse (n=20)	4.60±0.60	
The educational webinar made me more aware of the importance of ADR reporting	Pharmacist (n=63)	4.40±0.77	**0.039***
	Medical Doctor (n=14)	4.64±0.74	
	Dentist (n=6)	4.33±0.81	
	Nurse (n=20)	4.85±0.50	
The educational webinar helped me overcome barriers toward ADR reporting	Pharmacist (n=63)	4.24±0.83	**0.047***
	Medical Doctor (n=14)	4.07±0.82	
	Dentist (n=6)	3.83±1.16	
	Nurse (n=20)	4.70±0.57	
Following the educational webinar, I am confident with ADR reporting	Pharmacist (n=63)	4.38±0.70	**0.036***
	Medical Doctor (n=14)	4.50±0.52	
	Dentist (n=6)	3.83±0.75	
	Nurse (n=20)	4.00±0.47	
The educational webinar met my expectations	Pharmacist (n=63)	4.37±0.84	**0.039***
	Medical Doctor (n=14)	4.71±0.47	
	Dentist (n=6)	3.33±1.30	
	Nurse (n=20)	4.40±0.84	

*statistically significant results $p<0.05$

3.4.3 Second educational webinar – Participants demographics

The second educational webinar was attended by 90 HCPs. The evaluation form was completed by 73 participants. Participants distribution was 39 pharmacists (female n=23; male n=16), 17 medical doctors (female n=10; male n=7), and 17 nurses (female n=13; male n=4). The mean age for pharmacists was 36, for medical doctors 54 and for nurses 46. The mean years of practice for pharmacists was 13 years, for medical doctors 27 years and for nurses 20 years (Table 3.27).

Table 3.27 Evaluation form – Participants demographics (N=73)

	Gender		**Age (years)**	**Years of practice**
	Female (n)	*Male (n)*	*Mean ±SD*	*Mean ±SD*
Pharmacists (n=39)	23	16	36±10.98	13±11.03
Medical Doctors (n=17)	10	7	54±11.31	27±11.63
Nurses (n=17)	13	4	46±14.17	20±11.74

Most pharmacists who completed the evaluation form practiced in regulatory (n=19) and most of the medical doctors practiced in the hospital (n=7) and in private clinic (n=6). The majority of nurses (n=15) practiced in hospital (Table 3.28).

Table 3.28 Evaluation form – HCPs' distribution by area of practice (N=73)

	Pharmacists (n=39)		**Medical Doctors (n=17)**		**Nurses (n=17)**	
Area of practice	*n*	*%*	*n*	*%*	*n*	*%*
Community	15	38.5	2	11.8	3	17.6
Academia	3	7.7	4	23.5	0	0
Hospital	4	10.2	**7**	**41.1**	**15**	**88.2**
Industry	6	15.4	0	0	0	0
Regulatory	**19**	**48.7**	1	5.9	1	5.9
Nursing Home	0	0	0	0	0	0
Health Centre	0	0	0	0	0	0
Private Clinic	0	0	6	35.3	0	0

3.4.4 Evaluation of second educational webinar

With regards to the educational content, pharmacists, medical doctors and nurses strongly agreed that the sequence of material provided was appropriate, that the information was clearly presented and comprehensive, but the results were not statistically significant. Nurses significantly strongly agreed that the educational webinar made them more aware of the importance of ADR reporting (4.71; p=0.031) and that it helped them to overcome barriers toward ADR reporting (4.76; p=0.031). Medical doctors significantly agreed more than pharmacists and nurses that following the educational webinar they are more confident with ADR reporting (medical doctors 4.53; p=0.044). Nurses significantly strongly agreed more than pharmacists and medical doctors with the idea of the Safety Representative (4.88; p=0.024) (table 3.29).

Table 3.29 Evaluation of second educational webinar (N=73)

Statement	Profession	Mean ± SD	p-value
The sequence of material was appropriate	Pharmacist (n=39)	4.62±0.49	0.962
	Medical Doctor (n=17)	4.65±0.49	
	Nurse (n=17)	4.65±0.49	
Information in the educational webinar was clearly presented	Pharmacist (n=39)	4.67±0.53	0.547
	Medical Doctor (n=17)	4.82±0.39	
	Nurse (n=17)	4.76±0.44	
Information in the educational webinar was comprehensive	Pharmacist (n=39)	4.67±0.48	0.959
	Medical Doctor (n=17)	4.71±0.47	
	Nurse (n=17)	4.65±0.60	
The educational webinar was relevant for my practice	Pharmacist (n=39)	4.31±0.89	0.598
	Medical Doctor (n=17)	4.59±0.62	
	Nurse (n=17)	4.47±0.72	
The educational webinar made me more aware of the importance of ADR reporting	Pharmacist (n=39)	4.13±0.95	**0.031***
	Medical Doctor (n=17)	4.59±0.79	
	Nurse (n=17)	4.71±0.47	
The educational webinar helped me overcome barriers toward ADR reporting	Pharmacist (n=39)	4.18±0.88	**0.031***
	Medical Doctor (n=17)	4.47±0.80	
	Nurse (n=17)	4.76±0.44	
Following the educational webinar, I am confident with ADR reporting	Pharmacist (n=39)	4.31±0.73	**0.044***
	Medical Doctor (n=17)	4.53±0.51	
	Nurse (n=17)	3.94±0.66	
The educational webinar met my expectations	Pharmacist (n=39)	4.49±0.64	0.471
	Medical Doctor (n=17)	4.71±0.47	
	Nurse (n=17)	4.65±0.49	
I agree with the idea of the Safety Representative	Pharmacist (n=39)	4.31±0.83	**0.024***
	Medical Doctor (n=17)	4.53±0.62	
	Nurse (n=17)	4.88±0.33	

*statistically significant results $p<0.05$

Chapter 4

Discussion

4.1 Pharmacovigilance among Maltese healthcare professionals

Pharmacovigilance safeguards medicines safety and patient care by monitoring ADRs. By reporting ADRs, HCPs contribute to the overall knowledge of the safety profile of a medicinal product and to the national PhV system (Borg et al, 2018). The main objectives of the PhV system in place at the MMA include the evaluation, monitoring and communication of safety data related to a medicinal product and, when required, implementation of regulatory action with the aim of maximising benefits and minimising risks.[18] In this study, the total number of ICSRs received and processed from 2004 and 2019 by the MMA were reviewed.

Underreporting is considered the main limitation for ADR monitoring (Biagi et al, 2013). Since a correlation between knowledge and attitude and ADR reporting was found, this study aimed to assess knowledge and attitudes, together with practice and barriers, of HCPs practising in Malta towards ADR reporting. Since knowledge and attitude are modifiable factors which can have an effect on ADR reporting, educational interventions can fill the gaps in attitude and knowledge of HCPs and increase reporting rates (Lopez-Gonzalez et al, 2009).

The knowledge, attitude, practice and barriers of HCPs towards ADR were measured using a developed and validated questionnaire. Findings from the questionnaire revealed the need for more education and training on PhV/ADR reporting among pharmacists, medical doctors, nurses and dentists. Two educational webinars on PhV and ADR reporting were developed, validated and disseminated.

[18] Malta Medicines Authority [Internet]. Malta: Adverse Drug Reaction Reporting & Pharmacovigilance Guidance Notes For Healthcare Professionals; [cited 2021 May 05] Available from: http://www.medicinesauthority.gov.mt/file.aspx?f=4837

4.2 Adverse Drug Reaction reports received by the Malta Medicines Authority

The number of ADR reports received by the MMA, increased from 2004 till 2006, sharply increased between 2007 and 2010, remained stable until 2016 and sharply increased again between 2016 and 2018, when the highest number of ADR reports was registered. The increase of ADR reports is in part due to the ADR promotional activities organised by the MMA for both the HCPs and the patients with the aim to increase number and quality of ADR reports. In 2004, three seminars were held: one to launch the ADR reporting system, followed by two information sessions.[19] Between 2005 and 2006, measures to encourage ADR reporting by HCPs were taken and included the adoption of a self-addressed ADR reporting forms and the delivery of lectures.[20] The number of ADR reports received by the MMA dropped in 2007 but kept increasing until 2010. Between 2008 and 2009, lectures on ADR reporting and PhV continued to be delivered and this explains the increase in number of reports received.[21]

Between 2010 and 2016, no consistent changes in the number of reports received was seen. Following the introduction of Directive 2010/84/EU, between 2010 and 2012, the MMA reviewed its standard operating procedures relative to ADR reporting and redesigned the ADR reporting form, to be in line with the new legislation requirements. Further to this, the MMA also created content which it disseminated to HCPs to facilitate the understanding of this legislation at a local level. As a consequence of the new Directive, marketing authorisation holders were to send ADR reports directly to the EudraVigilance database, reducing the burden for the MMA.[22] In 2012, a simplified

[19] Malta Medicines Authority [Internet]. Malta: Annual Report 2004; [cited 2021 May 07] Available from: http://www.medicinesauthority.gov.mt/file.aspx?f=851
[20] Malta Medicines Authority [Internet]. Malta: Annual Report 2006; [cited 2021 May 07] Available from: http://www.medicinesauthority.gov.mt/file.aspx?f=143
[21] Malta Medicines Authority [Internet]. Malta: Annual Report 2009; [cited 2021 May 07] Available from: http://www.medicinesauthority.gov.mt/file.aspx?f=146
[22] Malta Medicines Authority [Internet]. Malta: Annual Report 2010; [cited 2021 May 07] Available from: http://www.medicinesauthority.gov.mt/file.aspx?f=147

electronic version of the ADR reporting form was developed that enabled patients to report adverse events.[23] In 2013, the MMA started a new campaign to promote ADR reporting, where the redesigned ADR reporting form was launched and distributed to the HCPs.[24]

Between 2015 and 2018, there was a higher influx of ADR reports reflecting a 3 year (2016-2018) strategy plan to promote ADR reporting. In 2015, the MMA started a promotional campaign of ADR reporting within the Medical School. Specially designed ADR reporting posters and videos were provided to this audience and MMA staff answered to questions made by students and HCPs.[25] In 2016, the MMA planned a 2 year ADR promotion strategy. The promotion strategy included a campaign which was part of a European initiative which aimed at providing national competent authorities with practical tools and guidance to develop and implement their PhV systems (Strengthening Collaboration for Operating Pharmacovigilance in Europe - SCOPE Joint Action) (Radecka et al, 2018). The first output was a social media campaign to encourage reporting of suspected ADRs.[26] In 2017, the MMA continued with its ADR promotion strategy started in 2016 and a conference on ADR reporting, safety of herbal medicinal products and medicines for children for consumers was organised. The MMA also launched an infographic campaign, where videos and other material were uploaded on the Authority's social media platform.[27] Between 2018 and 2019, five workshops on the

[23] Malta Medicines Authority [Internet]. Malta: Annual Report 2012; [cited 2021 May 07] Available from: http://www.medicinesauthority.gov.mt/file.aspx?f=531
[24] Malta Medicines Authority [Internet]. Malta: Annual Report 2013; [cited 2021 May 07] Available from: http://www.medicinesauthority.gov.mt/file.aspx?f=709
[25] Malta Medicines Authority [Internet]. Malta: Annual Report 2015; [cited 2021 May 07] Available from: http://www.medicinesauthority.gov.mt/file.aspx?f=2818
[26] Malta Medicines Authority [Internet]. Malta: Annual Report 2016; [cited 2021 May 07] Available from: http://www.medicinesauthority.gov.mt/file.aspx?f=3499
[27] Malta Medicines Authority [Internet]. Malta: Annual Report 2017; [cited 2021 May 07] Available from: http://www.medicinesauthority.gov.mt/file.aspx?f=3834

quality of ADR reporting for medical doctors were organised with the aim of improving the quality of information which was passed on in ADR reports.[28]

4.3 Knowledge of healthcare professionals about Adverse Drug Reaction reporting

Knowledge was measured using a validated questionnaire of 10 items, each of them containing 5 true or false questions. One point per each correct question was given, out of a total of 50 points.

In this study, HCPs had good knowledge on PhV and ADR reporting (mean knowledge score 42.02/50±3.90). Pharmacists (43.66/50) were significantly more knowledgeable on ADR reporting than the other HCPs ($p<0.001$). Studies reported similar knowledge levels of pharmacists (Xu et al, 2009; Su et al, 2010; Dorji et al, 2016; O'Callaghan et al, 2018; Hussain et al, 2021). Other studies revealed that pharmacists had lower knowledge about pharmacovigilance system and ADR reporting (Toklu and Uysal, 2008; Li et al, 2018; Suyagh et al, 2015).

4.4 Attitude of healthcare professionals towards Adverse Drug Reaction reporting

The attitude of HCPs was measured with 5 statements where the agreement was based on a Likert scale from 1 to 5. HCPs in this study showed a positive attitude towards ADR reporting. HCPs strongly agreed that reporting an ADR was important for medicinal products' safety and patient care (4.87) and that ADR reporting was part of their duty as HCPs (4.81) ($p<0.001$). The findings were in line with the ones of other studies (Pasier et al, 2009; Datta and Sengupta, 2015; Mendes Marques et al, 2016; Mulatu and Worku, 2017; AlShammari and Almoslem, 2018; Nisa et al, 2018; Adisa et al, 2019; Kassa Alemu and Biru, 2019; Hussain et al, 2021). No statistical significance between the four groups was found, meaning that perception that ADR reporting and consequent patient safety

[28] Malta Medicines Authority [Internet]. Malta: Annual Report 2019; [cited 2021 May 07] Available from: http://www.medicinesauthority.gov.mt/file.aspx?f=5005

enhancement was a shared responsibility among all healthcare professionals who should equally take the responsibility to report ADRs.

HCPs agreed that they wanted to confirm that it was the medicinal product causing the ADR before reporting the event (3.64) ($p<0.001$). Similar findings have been reported in other studies (Datta and Sengupta, 2015; Seid et al, 2018). Nurses (3.94), in this study, agreed more with the fact that before reporting an ADR they wanted to be sure that it was caused by that medicinal product ($p=0.002$). This finding agrees with a study conducted in Portugal (Mendes Marques et al, 2016).

HCPs disagreed with the statement "the single ADR I report does not contribute to the safety of that medicinal product" (2.00) ($p<0.001$). HCPs agree that even a single report can influence the overall knowledge of a medicinal product. These findings are in line with findings from other studies (De Angelis et al, 2015; AlShammari and Almoslem, 2018; Kassa Alemu and Biru, 2019). Results from a study conducted in Portugal showed that nurses believed that one single report would not make any difference to the safety knowledge of a medicinal product (Mendes Marques et al, 2016).

4.5 Practice of healthcare professionals towards Adverse Drug Reaction reporting

HCPs were asked to state if they have ever encountered an ADR and, if the answer was positive, to indicate the frequency with which they have encountered ADRs.

Despite good knowledge and a positive attitude, out of the HCPs of this study who encountered an ADR (65.8%, n=246), 30.1% (n=74) and 23.6 % (n=58) almost never or rarely reported the event respectively. Other studies have shown that the majority of HCPs did not report an ADR, even though they encountered it (Ekman and Bäckström, 2009; Mulatu and Worku, 2017; Laven et al, 2018; Nisa et al, 2018; Seid et al, 2018; Al Rabayah et al, 2019; Haines et al, 2020; Hussain et al, 2021).

Out of the HCPs who encountered an ADR (65.8%, n=246), 36.3% (n=45) of pharmacists almost never reported the event. The low rate of ADRs reported by pharmacists was found in another study conducted in United Kingdom (Green et al, 2001), in a study conducted in Germany (Laven et al, 2018), in a study conducted in Wales (Hughes and Weiss, 2019) and in a study conducted in Australia (Li et al, 2020). Most of the doctors (30.8%, n=16) stated that they rarely reported the event; while most of the nurses (31.2%, n=19) said that they almost always reported the event. This finding disagrees with an Italian study, where the percentage of nurses who reported an ADR during their practice was small (De Angelis et al, 2015). Another study conducted in Lahore showed that 79.5% of physicians and 58.8% of nurses have never reported an ADR; while 67.6% of pharmacists reported (Hussain et al, 2021). Results from a systematic review on nurses conducted by Salehi et al, revealed that, despite 67.7% of them encountering ADRs, only 21.2% of nurses actually reported the event (Salehi et al, 2021). This study showed that the majority of nurses (52.8%, n=68) have never encountered an ADR.

4.6 Barriers of healthcare professionals towards Adverse Drug Reaction reporting

While other studies assessed only knowledge, attitude and practice of HCPs towards ADR reporting to find out reasons for underreporting (Khan et al, 2013; Alshammari et al; 2015; Panja et al, 2015; Bhagavathula et al, 2016; Ali et al, 2018; Adisa et al, 2019; Haines et al, 2020), this study also identified barriers of HCPs towards ADR reporting. Out of a list of 11 items, the HCPs were asked to indicate what were the main reasons which stopped them from reporting an ADR.

The main reason for pharmacists not to report an ADR was ADRs being already well known and documented to occur (50.9%, n=85), followed by difficulty to understand whether an ADR occurred (45.5%, n=76) and lack of time (44.3%, n=74). Uncertainty of recognising ADRs and lack of time were barriers to reporting identified by other studies

(Wilbur, 2013; Cheema et al, 2017; Hussain et al, 2018; Li et al, 2018; Hughes and Weiss, 2019). Another barrier listed in the study of Cheema et al was the perception of community pharmacists that the ADR encountered was not serious enough to be reported (Cheema et al, 2017). The findings of this study disagree with the study conducted by Bahnassi and Al-Harbi, where pharmacists did not report an ADR because they did not know where to get the ADR reporting form from (Bahnassi and Al-Harbi, 2018). A study conducted in Malaysia revealed that lack of knowledge on how to report, unavailability of the ADR reporting form and not knowing where to send the ADR reporting form were the main barriers to reporting (Elkalmi et al, 2014).

ADRs being already well known and documented to occur (56.9%, n=33), difficulty to understand whether an ADR occurred (53.4%, n=31) and lack of time (48.3%, n=28) were the main barriers listed by medical doctors in this study and this finding is in line with another study (Ekman and Bäckström, 2009). Besides the barriers found in this study, Nadew et al reported that the barriers encountered by medical doctors while reporting an ADR were: lack of awareness and training on risks related to underreporting, lack of encouragement, delay and/or absence of feedback on the reported ADRs from the national PhV centre, fear of legal liability, and lack of communication between patient and medical doctors (Nadew et al, 2020).

The barriers listed by dentists in this study were: ADRs being already well known and documented to occur (55%, n=11), difficulty to understand whether an ADR occurred (50%, n=10) and not knowing where to send the ADR reporting form (45%, n=9). The findings differ from the study of Khan et al, where lack of awareness about ADR monitoring centre and PhV program existence, complacency, lack of training and fear were found to be the main barriers to ADR reporting by dentists (Khan et al, 2015). A study conducted on medical doctors and dentists showed that barriers to ADR reporting

were: concern that the report might be wrong, limited information given by the patients, lack of confidence to discuss the cases encountered and fear of the ADR report having a negative impact on the manufacturing company of the medical product (Jnaneswar et al, 2020).

Barriers encountered by nurses in this study were: difficulty to understand whether an ADR occurred (54.3%, n=70), not knowing where to send the ADR reporting form (36.4%, n=47) and difficulty in accessing the ADR reporting form (34.1%, n=44). Similarly, a study conducted in Italy, found that barriers encountered by nurses when reporting an ADR were: where to find the ADR reporting form, where to send it and how to fill it in (De Angelis et al, 2015). Conversely, the study conducted by Hussain et al, revealed that barriers towards reporting included lack of a proper ADR reporting system, work overload and the fear of having legal implications (Hussain et al, 2020). Results from a review by Salehi et al, disclosed that lack of training was the most common barrier to ADR reporting, followed by ADRs being already well known, lack of information provided by patients, difficulty in accessing the ADR reporting form, fear to have legal implications following ADR reporting and lack of time (Salehi et al, 2021).

4.7 Education and training on Adverse Drug Reaction reporting

Le et al in his study stated that better knowledge and a positive attitude can improve ADR reporting (Le et al, 2020). Results from other studies showed that better knowledge on ADR reporting encouraged HCPs to report an ADR (Lopez-Gonzalez et al, 2009; Liu et al, 2015) and ADR reporting rates were greater when the attitude was more positive (Herdeiro et al, 2005; Herdeiro et al, 2006). Educational interventions targeting HCPs may effect reporting behaviour through improving knowledge and changing attitudes towards ADR reporting (Lopez-Gonzalez et al, 2013; Pagotto et al, 2013). Results from previous studies revealed that continuing educational programs for HCPs could improve

knowledge and change attitudes of HCPs towards ADR reporting (Figueiras et al, 2006; Varallo et al, 2017; Lemay et al, 2018), thus ADR reporting quality and quantity (Mulchandani and Kakkar, 2019; Khalili et al, 2020). Reumerman et al stated that continuing educational interventions should be done in undergraduate curricula for HCPs (Reumerman et al, 2018).

Despite studies revealing that underreporting of ADRs can be directly related to poor knowledge and negative attitudes (Nisa et al, 2018; Adisa and Omitogun, 2019; Güner and Ekmekci, 2019; Haines et al, 2020), HCPs participating in this study had good knowledge and a positive attitude. Practice towards ADR reporting was not sufficient, as the majority of HCPs did not report an ADR (53.7%, n=132). Difficulty to understand whether an ADR occurred and ADRs being already well known and documented to occur, could be the reasons for underreporting in this study. Education and training may be helpful to improve/increase the awareness of HCPs about the importance of ADR reporting (Al Rabayah et al, 2019) and overcome barriers (Biagi et al, 2013; Cheema et al, 2017; Lemay et al, 2018; Salehi et al, 2021).

The majority of HCPs in this study wanted to receive more education on ADR reporting (strongly agree: 40.4%, n=151; agree 31.8%, n=119). Interest in further education and training about ADR reporting is also found in other studies (Chema et al, 2017; Hajj et al; 2018; Hussain et al, 2018; Li et al, 2018; Aldryhim et al, 2019; Adenuga et al, 2020; Nisa et al, 2020). In this study, nurses (4.41) significantly strongly agreed more than the other HCPs that they required more education on ADR reporting ($p<0.001$). This finding is in line with a study of De Angelis et al where nurses were willing to develop their knowledge and competencies in ADR reporting (De Angelis et al, 2015) and with other studies (Hanafi et al, 2014; Adisa and Omitogun, 2019). A review from Salehi et al

revealed that nurses were not adequately prepared to report an ADR and wanted to receive more education about it (Salehi et al, 2021).

HCPs in this study preferred continuing professional education seminars (65.8%, n=246) and guidelines/publications (56.4%, n=211) as a principal method for acquiring more education on ADR reporting. Preference in following continuing educational seminars and reading guidelines was similarly reported in other studies (Pimpalkhute et al, 2012; Aldryhim et al, 2019); while lectures (Sanghavi et al, 2013; Hajj et al; 2018) and workshops (Herdeiro et al, 2012; Khan et al, 2015; Ribeiro-Vaz, 2016) were preferred in other studies.

Two educational webinars *Pharmacovigilance in the time of a pandemic crisis – adverse drug reaction reporting* and *Pharmacovigilance in the time of a pandemic crisis – adverse drug reaction reporting – part 2 Outcomes* were developed reflecting findings from the questionnaire, in which HCPs stated that they wanted to receive more education and training on ADR reporting; hence two educational webinars using clinical case studies were organised. The case studies were selected to help HCPs identify ADRs related to Pfizer-Biontech, Astrazeneca, Moderna, the Covid-19 vaccines newly developed and approved at the time of the educational webinars.

HCPs agreed that the two educational webinars made them more aware of the importance of ADR reporting and helped them overcome barriers towards ADR reporting, with significantly higher agreement by nurses compared to the other HCPs ($p<0.05$). HCPs agreed that, following the educational webinars, they are more confident with ADR reporting, with significantly higher agreement by pharmacists and medical doctors ($p<0.05$). Other studies reported increased awareness and confidence on ADR reporting

following educational programs (Jha, 2014; Ganesan et al, 2017; Varallo et al, 2017; Shutte et al, 2018; Opadeyi et al, 2019; Shrestha et al, 2020).

In this study, nurses significantly agreed more than pharmacists and medical doctors with the idea of having a Safety Representative to help increase the quantity and quality of ADR reports and overcome barriers towards ADR reporting (4.88; p=0.024). The role of the Safety Representative was described in the educational webinars. Safety Representatives would be pharmacists who work closely with HCPs, to promote safe use of medical products and guide HCPs to correctly report ADRs and this can be done using emails, SMS, educational seminars, workshops. A study by Mulchandani and Kakkar suggested that periodic emails and/or SMS are an inexpensive and effective way to remember and encourage HCPs to report ADRs (Mulchandani and Kakkar, 2019). One of the roles suggested for the Safety Representative is creating a bridge between the NCA and the HCPs. A study by Pimpalkhute et al, revealed that developing an harmonious relationship between PhV centres and HCPs is the key for long term success of educational programs (Pimpalkhute et al, 2012). Studies show that the ADR reporting decreases if educational interventions are not regularly held. Results of a study from Varallo et al revealed that the number of ADR reports decreased again after four months following the educational intervention. A decrease following an educational intervention is also seen in another study (Lopez-Gonzalez, 2015). It is suggested that educational interventions are organised periodically to maintain motivation among HCPs when it comes to ADR reporting (Vassallo et al, 2017).

4.8 Limitations of the study

Only ADR reports received by the MMA were analysed in this study. MAHs can also receive ADR reports influencing results regarding the annual number of ADR reports

registered in Malta per year, changing the number of ADR reports registered in Malta per year.

Dissemination of the questionnaire assessing knowledge, attitude, practice and barriers of HCPs towards ADR reporting, educational webinars and evaluation forms was mainly carried out through social media due to a decrease of accessibility to HCPs due to Covid-19 related restrictions.

The proportion of HCPs who participated in this study was not equal: the number of medical doctors and dentists was low compared to the number of pharmacists and nurses.

After the two educational webinars, HCPs were asked to answer an evaluation form, rating, on a Likert-scale, their agreement or disagreement to some questions. Some of the answers of the HCPs might have been biased.

4.9 Recommendations for further study

A review involving ADR reports received by both the MMA and marketing authorisation holders should be performed.

Further studies involving a larger number of HCPs is suggested to explore knowledge, attitude, practice and barriers of a larger sample size of HCPs working in Malta.

The data collected from the questionnaire assessing knowledge, attitude, practice and barriers of HCPs towards ADR reporting could be used and discussed by stakeholders/the national competent authority in a focus group to plan regular interactive educational programs for HCPs.

The positive feedback obtained from the two educational webinars could serve as a pilot to promote the idea of the Safety Representative.

Future educational webinars/seminars on medicinal products, other than vaccines, are needed.

4.10 Conclusion

The study revealed that HCPs participating in this study were knowledgeable about ADR reporting and had a positive attitude towards ADR reporting. Some HCPs admitted not to report ADRs. The main reason for not reporting was difficulty to understand whether an ADR occurred, followed by ADRs being already well known and documented to occur. HCPs agreed in receiving more education and training about ADR reporting.

Educational webinars, such as the ones conducted in this study, helped increase and improved awareness on the importance of quality ADR reporting which can lead to an increase in the number of ADR reports and better PhV practices which can positively impact patient care and patient quality of life.

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Appendices

Appendix 1: Validation tool of questionnaire

Questionnaire validation

Introduction and Instructions

You are invited to participate in the **validation** of a questionnaire which aims to assess knowledge, attitude, practice, barriers, and education about adverse drug reaction reporting among healthcare professionals practising in Malta. The questionnaire developed is part of a research project titled "An innovative approach to Pharmacovigilance" being undertaken by Doctorate in Pharmacy student Elisa Curtolo.

You are requested to complete the following **validation tool** to rate the **relevance** and **clarity** of each question and the **layout** of the questionnaire, on a Likert scale of 1 to 5.

i. **Relevance** to research topic: 1 (not relevant) – 5 (very relevant)

ii. **Clarity** of questions and statements: 1 (not clear) – 5 (very clear)

iii. **Structure and Layout** of the questionnaire: 1 (not well structured) – 5 (very well structured)

Please provide comments and suggestions in the dedicated section.

Kindly state if you think question should be retained using Yes/No answer.

SECTION 1: PARTICIPANT DEMOGRAPHICS

1. **Gender** ☐ Male ☐ Female ☐ Other

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

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_____
_____

2. **Age (years)** ☐ 21-35 ☐ 36-45 ☐ 46-55 ☐ 56-69 ☐ 70+

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

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3. **Profession**

☐ Pharmacist ☐ Medical Doctor ☐ Dentist ☐ Nurse

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

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_____
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4. **Area of specialisation:**

_____

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

_____
_____
_____

5. **Area of practice**

☐ Community ☐ Academia

☐ Hospital ☐ Industry

☐ Regulatory ☐ Nursing Home

☐ Health Centre

☐ Other _____

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

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6. **Years of practice** ☐ < 2 ☐ 2-5 ☐ 6-10 ☐ 10-20 ☐ >20

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

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SECTION 2: KNOWLEDGE ABOUT ADVERSE DRUG REACTION (ADR) REPORTING

For each of the following questions, indicate which statement is TRUE and which one is FALSE, by marking the appropriate box.

7. What is the scope of Pharmacovigilance?	TRUE	FALSE
a) To monitor a genetic response to a medicinal product		
b) To determine the price of the medicinal products		
c) To audit the performance of healthcare professionals (HCPs)		
d) To monitor ADRs		
e) To promote patient safety and effective use of medicinal products		

Comments/views_____
_____
_____

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

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_____
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8. Which of these statements about ADRs is **true**?	TRUE	FALSE
a) An ADR is a medicinal product manufactured out of specifications		
b) An ADR is when a prescription medicinal product is dispensed without a prescription		
c) An ADR can be predicted and expected		
d) An ADR can occur at doses normally used		
e) An ADR could be a side effect which may occur when taking a medicinal product		

Comments/views_____

_____

_____

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

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9. **What** type of ADRs should be reported by HCPs?	TRUE	FALSE
a) All suspected ADRs to all medicinal products and vaccines		
b) ADRs which cause mortality		
c) ADRs which cause or prolong hospitalisation		
d) Only ADRs which result in persistent or significant disability		
e) Only ADRs related to newly marketed medicinal products		

Comments/views_____

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	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

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10. Who can report an ADR?	TRUE	FALSE
a) Medical Doctors		
b) Pharmacists		
c) Nurses		
d) Patients		
e) Dentists		

Comments/views_____

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_____

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

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_____

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11. How can ADRs be reported?	TRUE	FALSE
a) On an ADR reporting form found on the University website		
b) On an ADR reporting form found on the Marketing Authorisation Holder (MAH) website		
c) On an ADR reporting form found on the Ministry of Health website		
d) On an ADR reporting form found on the Malta Medicines Authority (MMA) website		
e) On an ADR reporting form found on the Malta Police Force website		

Comments/views_____

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_____

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

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12. What needs to be included in an ADR report?	TRUE	FALSE
a) Information about the suspected ADR and the patient		
b) Details about all the members of the family of the patient		
c) Details about an identifiable reporter		
d) Police conduct certificate of the patient		
e) Information about the suspected medicinal product causing the ADR		

Comments/views_____

_____

_____

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

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13. <u>How</u> should an ADR reporting form be filled in?	TRUE	FALSE
a) All the sections should be filled in		
b) Only section with information about ADR (section 1) and section with details of reporter (section 3) should be filled in		
c) Only section with information about ADR (section 1) and section with information about medication error (section 2) should be filled in		
d) Only section with information about medication error (section 2) and section with details of reporter (section 3) should be filled in		
e) Only section with information about ADR (section 1) should be filled in		

Comments/views_____

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	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

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14. **Where** should the ADR reporting form be sent?	TRUE	FALSE
a) To the Local Council		
b) To the MMA via free postage		
c) To the MAH or its local representative		
d) To the MMA via email		
e) To the local veterinary surgeon		

Comments/views_____

_____

_____

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

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15. How does the MMA **manage** the ADR reports?	TRUE	FALSE
a) A pharmacist of the Post-Licensing Department reads the ADR report and discards it immediately after		
b) A pharmacist of the Post-Licensing Department validates the ADR report, evaluates its information and sends it to Eudravigilance		
c) A pharmacist of the Post-Licensing Department sends the ADR report to the Police for further action		
d) A pharmacist of the Post-Licensing Department reports the adverse effect to the Prime Minister		
e) A pharmacist of the Post-Licensing Department withdraws the medicinal product from the market		

Comments/views_____

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_____

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

_____

_____

16. What is the **impact** of ADR reporting?	TRUE	FALSE
a) Regulatory actions, such as a change in the product information, suspension or withdrawal from the market, can be taken		
b) A change in the product information could result		
c) The withdrawal of the medicinal product from the market always results		
d) The suspension of the medicinal product from the market always results		
e) A decrease of the price of the medicinal product is recommended		

Comments/views_____

_____

_____

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

_____

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_____

SECTION 3: ATTITUDE TOWARDS ADR REPORTING IN MALTA

On a Likert scale of 1 (strongly disagree), 2 (disagree), 3 (neutral), 4 (agree) to 5 (strongly agree), rate the following statements by marking the appropriate box with a "X".

17.	Reporting is important for medicinal products safety and patient care

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

_____

_____

_____

18.	ADR reporting is part of my duty as a HCP

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

_____

_____

_____

19.	The single ADR I report does not contribute to the safety of that medicinal product

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

_____

_____

_____

20.	Before reporting any ADR, I want to be sure that the ADR is caused by the medicinal product

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

_____

_____

_____

21.	I think there should be an appointed person to report an ADR

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

_____

_____

_____

22.	Remuneration for ADR reporting could encourage me to report

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

_____

_____

_____

SECTION 4: PRACTICE TOWARDS ADR REPORTING

23. How many cases of patients experiencing ADRs have you encountered?

☐ No cases ☐ Daily ☐ Weekly ☐ Monthly ☐ Yearly

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

_____

_____

_____

24. How often have you reported an ADR when encountered?

☐ Daily ☐ Weekly ☐ Monthly ☐ Yearly

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

_____

_____

_____

SECTION 5: BARRIERS TO ADR REPORTING

*Between the following statements, choose which ones are the most significant reasons which stop you from reporting an ADR. You may select **more than one** option.*

☐ Limited understanding of its value

☐ Difficulty in accessing ADR reporting form

☐ Lack of time

☐ Lack of motivation

☐ Fear of consequences

☐ Not knowing where to send the ADR reporting form

☐ Concern that ADR reporting may generate extra work

☐ Difficulty to understand whether an ADR as occurred or not

☐ Patient followed up by different professionals

☐ Others (*Please specify)*_____

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

_____

_____

_____

SECTION 6: EDUCATION AND TRAINING ON ADR REPORTING

On a Likert scale of 1 (strongly disagree), 2 (disagree), 3 (neutral), 4 (agree) to 5 (strongly agree), rate the following statements by marking the appropriate box with a "X".

26.	I believe I am competent in the area of ADR reporting

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

_____

_____

_____

27.	I require more education on ADR reporting

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

_____

_____

_____

28. a) How would you prefer to receive updates on ADR reporting?
*(you may select **more than one** option):*

☐ Continuing professional education seminars ☐ Courses

☐ Conferences ☐ Workshops

☐ Guidelines/Publications ☐ I am not interested

☐ Others (*Please specify)*_____

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

_____

_____

_____

b) How would you prefer to follow the selected learning activities in question 28a?
*(you may select **more than one** option)*

☐ Attending in person

☐ Following the learning activities online

☐ A combination of both

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

_____

_____

_____

c) Which topic/s would you like to follow during the selected learning activities in 28a?
*(you may select **more than one** option)*

☐ ADR reporting ☐ Medication errors

☐ How ADR reporting contributes to drug safety

☐ Others, suggestions (*Please specify)*_____

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

_____
_____
_____

d) What day and time of the week would you prefer the learning activity in 28a to be held? How long would you like that the learning activity to last?

Day of the week _____

Time _____

N° of hours per session_____

N° of sessions _____

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

_____
_____
_____

29. Other comments/recommendations:

_____

_____

_____

_____

_____

	1	2	3	4	5
Relevance	☐	☐	☐	☐	☐
Clarity	☐	☐	☐	☐	☐

Do you think this question should be retained? ☐ Yes ☐ No

Comments/Recommendations:

_____

_____

_____

Rate the **layout** of the questionnaire: 1 (not well structured) – 5 (very well structured)

	1	2	3	4	5
Structure and Layout	☐	☐	☐	☐	☐

Thank you

Appendix 2: Ethics approval

L-Università ta' Malta

Elisa Curtolo <elisa.curtolo.18@um.edu.mt>

FRECMDS_2021_002 - FOR RECORDS - ELISA CURTOLO

9 messages

FACULTY RESEARCH ETHICS COMMITTEE <research-ethics.ms@um.edu.mt> 12 October 2020 at 11:53
To: Elisa Curtolo <elisa.curtolo.18@um.edu.mt>
Cc: Professor Anthony Serracino Inglott <anthony.serracino-inglott@um.edu.mt>

Dear Elisa Curtolo,

Thank you for your confirmation.

L-Università ta' Malta

Ruth Stivala | Secretary
B.A.(Hons)(Melit.),M.A.(Melit.)

Faculty Research Ethics Committee
Faculty of Medicine and Surgery
Medical School, Mater Dei Hospital
+356 2340 1214
https://www.um.edu.mt/ms/students/researchethics

On Thu, 8 Oct 2020 at 15:37, Elisa Curtolo <elisa.curtolo.18@um.edu.mt> wrote:

> Dear Ms Stivala,
>
> I confirm I have attached all the documents that I mentioned.
>
> Thank you.
>
> Kind regards,
> Elisa Curtolo
>
> On Wed, 7 Oct 2020 at 12:08, FACULTY RESEARCH ETHICS COMMITTEE <research-ethics.ms@um.edu.mt> wrote:
>
> > Dear Elisa Curtolo,
> >
> > Since your self-assessment resulted in no issues being identified, FREC will file your application for record and audit purposes but will not review it.
> >
> > You may proceed with your study.
> >
> > Any ethical and legal issues including data protection issues are your responsibility and that of your supervisor.
> >
> > Kindly confirm that you sent all the documents which you attached to the UREC form and also other documents related to your study for audit purposes.

L-Università ta' Malta

Ruth Stivala | Secretary
B.A.(Hons)(Melit.),M.A.(Melit.)

Faculty Research Ethics Committee
Faculty of Medicine and Surgery
Medical School, Mater Dei Hospital
+356 2340 1214
https://www.um.edu.mt/ms/students/researchethics

On Wed, 7 Oct 2020 at 11:32, Elisa Curtolo <elisa.curtolo.18@um.edu.mt> wrote:

> Dear Ms Stivala,
>
> I am attaching to this email **UREC FORM V_15062020 6409 "For FREC Records".**
>
> I am Elisa Curtolo, a third year Doctorate in Pharmacy student.
>
> Please find attached in a zip folder *proposal, protocol, UREC form, my CV, a questionnaire, and a recruitment letter* as part of my research project titled "An Innovative approach to Pharmacovigilance" under the supervision of Professor Anthony Serracino-Inglott.
>
> Thank you.
>
> Kind regards,
> Elisa Curtolo

Appendix 3: Final version of questionnaire assessing knowledge, attitude, practice, barriers and need for more education of HCPs on ADR reporting

An innovative approach to Pharmacovigilance

Elisa Curtolo

PharmD student

Department of Pharmacy, University of Malta

Introduction and Instructions

Dear Participant,

You are invited to participate in a research project entitled "An innovative approach to Pharmacovigilance". This research is being conducted by Elisa Curtolo as part of the Doctorate in Pharmacy degree at the Departement of Pharmacy, University of Malta, under the supervision of Professor Anthony Serracino-Inglott and Dr Janis Vella Szijj.

The questionnaire developed aims to assess knowledge, attitude, practice, barriers and education about adverse drug reaction reporting among healthcare professionals practising in Malta.

All healthcare professionals are eligible to participate.

You are invited to complete the attached questionnaire. Questionnaire responses will only be accessed by research team members. The questionnaire should be completed without consulting reference material. Participation is voluntary and the estimated time of completion of the questionnaire is 10 minutes.

Should you have any queries, kindly contact the researcher Elisa Curtolo:
Email: elisa.curtolo.18@um.edu.mt
Contact number: +393460911347

Thank you very much for your participation

SECTION 1: PARTICIPANT DEMOGRAPHICS

1. **Gender** ☐ Male ☐ Female ☐ Other

2. **Age (years)** ☐ 21-35 ☐ 36-45 ☐ 46-55 ☐ 56-69 ☐ 70+

3. **Profession**

   ☐ Pharmacist ☐ Medical Doctor ☐ Dentist ☐ Nurse

4. **Area of specialisation** *(if applicable):*

   _____

5. **Area of practice** (*You may select **more than one** option*)

   ☐ Community Pharmacy ☐ Academia

   ☐ Hospital ☐ Industry

   ☐ Regulatory ☐ Nursing Home

   ☐ Health Centre ☐ Private Clinic

   ☐ Other _____

6. **Years of practice** ☐ < 2 ☐ 2-5 ☐ 6-10 ☐ 11-20 ☐ >20

SECTION 2: KNOWLEDGE ABOUT ADVERSE DRUG REACTION (ADR) REPORTING IN MALTA

For each of the following questions, indicate which statement is TRUE and which one is FALSE, by marking the appropriate box.

7. What is the **scope** of Pharmacovigilance?	TRUE	FALSE
a) To monitor a genetic response to a medicinal product		
b) To determine the price of the medicinal products		
c) To audit the performance of healthcare professionals (HCPs)		
d) To monitor the occurrence of ADRs		
e) To promote patient safety and effective use of medicinal products		

Comments/views_____

_____

_____

8. Which of these statements about ADRs is **true**?	TRUE	FALSE
a) An ADR is a medicinal product manufactured out of specifications		
b) An ADR is when a prescription medicinal product is dispensed without a prescription		
c) An ADR can be predicted and expected		
d) An ADR can occur at doses normally used		
e) An ADR could be a side effect which may occur when taking a medicinal product		

Comments/views_____

_____

_____

9. **What** type of ADRs should be reported by HCPs?	TRUE	FALSE
a) All suspected ADRs to all medicinal products and vaccines		
b) ADRs which cause mortality		
c) ADRs which cause or prolong hospitalisation		
d) Only ADRs which result in persistent or significant disability		
e) Only ADRs related to newly marketed medicinal products		

Comments/views_____

_____

_____

10. Who can report an ADR?	TRUE	FALSE
a) Medical Doctors		
b) Pharmacists		
c) Nurses		
d) Patients/Consumers		
e) Dentists		

Comments/views_____

_____

_____

11. How can ADRs be reported?	TRUE	FALSE
a) On an ADR reporting form found on the University of Malta website		
b) On an ADR reporting form found on the Marketing Authorisation Holder (ΜΑΗ) website		
c) On an ADR reporting form found on the Ministry of Health website		
d) On an ADR reporting form found on the Malta Medicines Authority (MMA) website		
e) On an ADR reporting form found on the Malta Police Force website		

Comments/views_____

_____

_____

12. What needs to be included in an ADR report?	TRUE	FALSE
a) Information about the suspected ADR		
b) Details about all the members of the family of the patient		
c) Details about an identifiable reporter		
d) Information about the patient		
e) Information about the suspected medicinal product causing the ADR		

Comments/views_____

_____

_____

13. How should an ADR reporting form be filled in?	TRUE	FALSE
a) All the sections should be filled in		
b) Only section with information about ADR (section 1) and section with details of reporter (section 3) should be filled in		
c) Only section with information about ADR (section 1) and section with information about medication error (section 2) should be filled in		
d) Only section with information about medication error (section 2) and section with details of reporter (section 3) should be filled in		
e) Only section with information about ADR (section 1) should be filled in		

Comments/views_____

_____

_____

14. Where should the ADR reporting form be sent?	TRUE	FALSE
a) To the Local Council		
b) To the MMA by post		
c) To the MAH or its local representative		
d) To the MMA via email		
e) To the local veterinary surgeon		

Comments/views_____

_____

_____

15. How does the MMA **manage** the ADR reports?	TRUE	FALSE
a) A pharmacist from the Post-Licensing Department reads the ADR report and discards it immediately after		
b) A pharmacist from the Post-Licensing Department validates the ADR report, evaluates its information and sends it to Eudravigilance		
c) A pharmacist from the Post-Licensing Department sends the ADR report to the Police for further action		
d) A pharmacist from the Post-Licensing Department contacts the patient		
e) A pharmacist from the Post-Licensing Department withdraws the medicinal product from the market		

Comments/views_____

_____

_____

16. What is the **impact** of ADR reporting?	TRUE	FALSE
a) Regulatory actions, such as a change in the product information, suspension or withdrawal from the market, can be taken		
b) An ADR can bring about a change in the summary of product information		
c) An ADR always brings about a withdrawal of the product from the market		
d) An ADR always brings about the suspension of the product from the market		
e) A decrease of the price of the medicinal product is recommended		

Comments/views_____

_____

_____

SECTION 3: ATTITUDE TOWARDS ADR REPORTING IN MALTA

On a Likert scale of 1 (strongly disagree), 2 (disagree), 3 (neutral), 4 (agree) to 5 (strongly agree), rate the following statements by marking the appropriate box with a "X".

N°	Statement	1 (Strongly disagree)	2 (Disagree)	3 (Neutral)	4 (Agree)	5 (Strongly agree)
Attitude						
17.	Reporting is important for medicinal products safety and patient care					
18.	ADR reporting is part of my duty as a HCP					
19.	The single ADR I report does not contribute to the safety of that medicinal product					
20.	Before reporting any ADR, I want to be sure that the ADR is caused by the medicinal product					
22.	Remuneration for ADR reporting could encourage me to report					

SECTION 4: PRACTICE TOWARDS ADR REPORTING

23. How often do you encounter patients experiencing ADRs?

☐ No cases ☐ Daily ☐ Weekly ☐ Monthly ☐ Yearly

24. How often have you reported an ADR when encountered?

☐ Almost never ☐ Rarely ☐ Sometimes ☐ Very frequently ☐ Almost always

SECTION 5: BARRIERS TO ADR REPORTING

25. *Between the following statements, choose which ones are the most significant reasons which stop you from reporting an ADR. You may select* ***more than one*** *option.*

☐ Limited understanding of its value

☐ Difficulty in accessing ADR reporting form

☐ Lack of time

☐ Lack of motivation

☐ Fear of consequences

☐ Not knowing where to send the ADR reporting form

☐ Concern that ADR reporting may generate extra work

☐ Difficulty to understand whether an ADR as occurred or not

☐ Patient followed up by different professionals

☐ ADR already well known and documented to occur

☐ Not being aware that ADRs may be reported

☐ Others (*Please specify)*_____

SECTION 6: EDUCATION AND TRAINING ON ADR REPORTING

On a Likert scale of 1 (strongly disagree), 2 (disagree), 3 (neutral), 4 (agree) to 5 (strongly agree), rate the following statements by marking the appropriate box with a "X".

N°	Statement	1 (Strongly disagree)	2 (Disagree)	3 (Neutral)	4 (Agree)	5 (Strongly agree)
Education and Training						
26.	I believe I am competent in the area of ADR reporting					
27.	I require more education on ADR reporting					

28. a) How would you prefer to receive updates on ADR reporting?
*(you may select **more than one** option):*

☐ Continuing professional education seminars ☐ Courses

☐ Conferences ☐ Workshops

☐ Guidelines/Publications ☐ I am not interested

☐ Others (*Please specify)*_____

b) How would you prefer to follow the selected learning activities in question 28a?
*(you may select **more than one** option)*

☐ Attending in person

☐ Following the learning activities online

☐ A combination of both

c) Which topic/s would you be most interested in during the selected learning activities in 28a?
*(you may select **more than one** option)*

☐ ADR reporting ☐ Medication errors

☐ How ADR reporting contributes to drug safety

☐ Others, suggestions (*Please specify)*_____

d) What day and time of the week would you prefer the learning activity in 28a to be held? How long would you like that the learning activity to last?

Day of the week _____

Time _____

N° of hours per session_____

N° of sessions _____

29. Other comments/recommendations:

_____

_____

_____

_____

_____

Appendix 4: Invitations

L-Università ta' Malta

PHARMACOVIGILANCE IN THE TIME OF A PANDEMIC CRISIS - ADVERSE DRUG REACTION REPORTING

Educational Webinar

Monday 22 February 2021

at 8:30 pm

Elisa Curtolo

Doctorate in Pharmacy student

Department of Pharmacy, University of Malta

L-Università ta' Malta

PHARMACOVIGILANCE IN THE TIME OF A PANDEMIC CRISIS - ADVERSE DRUG REACTION REPORTING - Part 2 Outcomes

Educational Webinar

Monday 15 March 2021

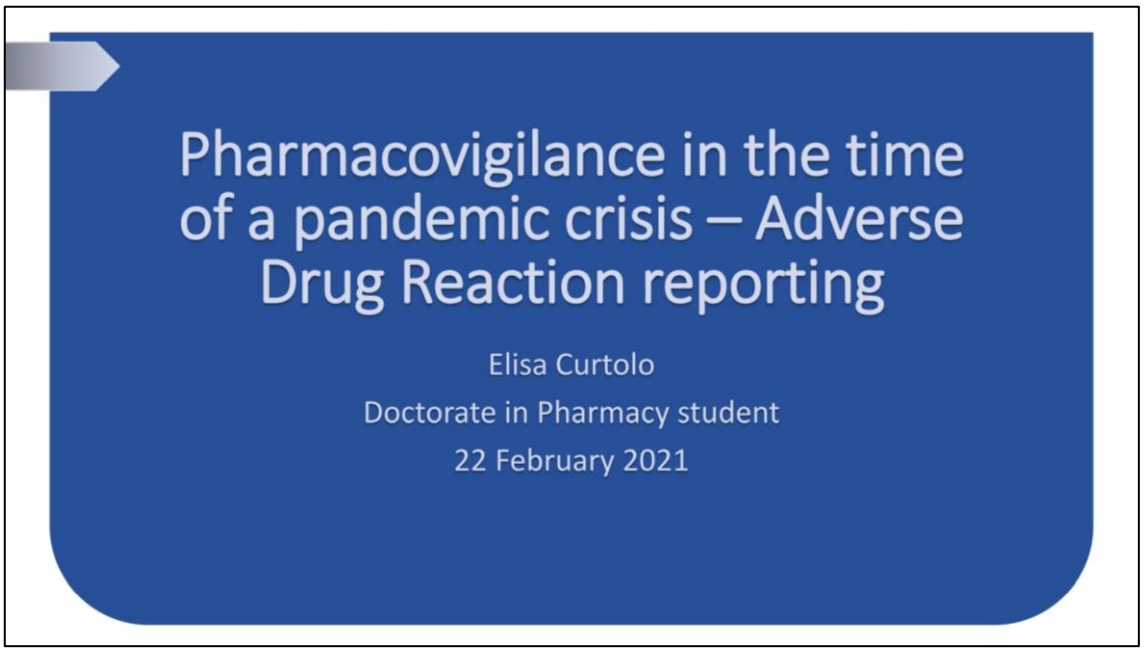
8:30 pm

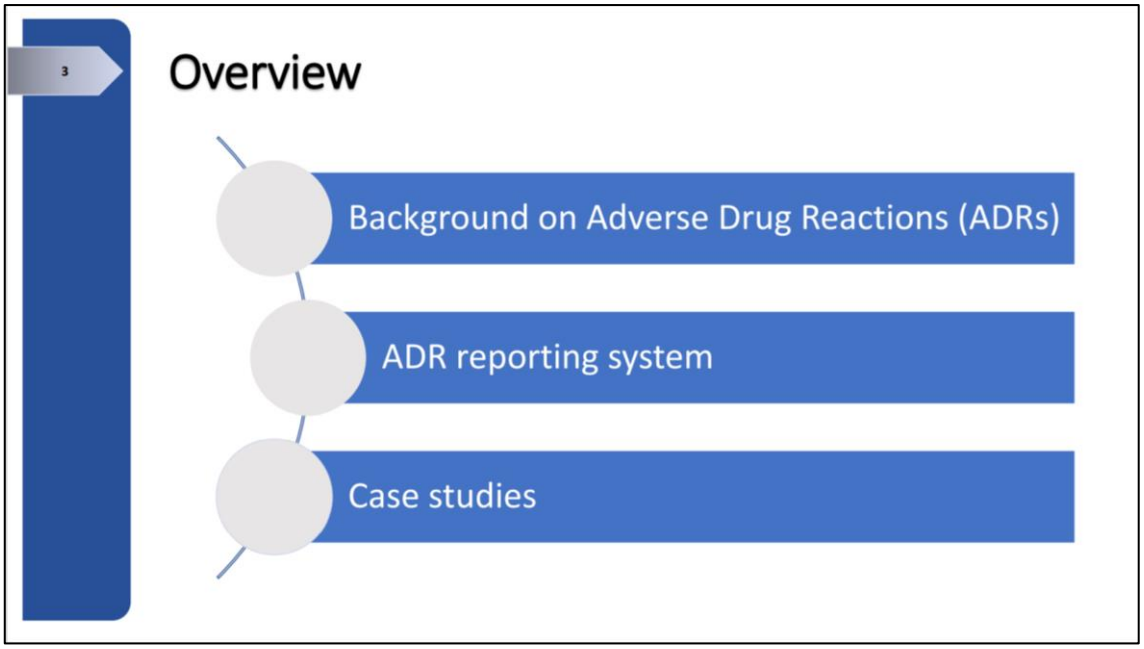
Elisa Curtolo

Doctorate in Pharmacy candidate

Department of Pharmacy, University of Malta

Appendix 5: Educational webinars slides on *Pharmacovigilance in the time of a pandemic crisis – adverse drug reaction reporting* part 1 and part 2





Background on Adverse Drug Reactions (ADRs)

5

ADRs

- One of the leading causes of **morbidity**, **mortality**, and **poor therapeutic outcomes**
- Increase hospital admissions and health care costs

Khalil H, Huang C. Adverse drug reactions in primary care: a scoping review. BMC Health Serv Res. 2020;20(1):5

6

ADRs

Statistics:

- Median % of hospital admissions due to an ADR: **3.5 %**
- Median % of patients who experienced an ADR during hospitalisation: **10.1 %**
- ADRs are the cause of **~ 197,000** deaths in Europe annually

Bouvy JC, De Bruin ML, Koopmanschap MA. Epidemiology of adverse drug reactions in Europe: a review of recent observational studies. Drug Saf. 2015;38(5):437-53

7

ADR - Definition

2 CAP. 458.] *MEDICINES*

Short title. 1. The short title of this Act is the Medicines Act.

PART I

PRELIMINARY

Interpretation. *Amended by: III. 2004.44; XI. 2007.2; V. 2013.2.* 2. In this Act, unless the context otherwise requires -

"adverse reaction" means a response to a medicinal product which is noxious and unintended;

"advertising" in relation to medicinal products includes any form of door-to-door information, canvassing activity or inducement designed to promote the prescription, supply, sale or consumption of medicinal products and without prejudice to the generality of the foregoing in particular includes:

(*a*) the advertising of medicinal products to the general public;

(*b*) the advertising of medicinal products to persons qualified to prescribe or supply them;

(*c*) visits by medical or sales representatives to persons qualified to prescribe medicinal products;

(*d*) the supply of samples;

(*e*) the provision of inducements to prescribe or supply medicinal products, by way of a gift, offer or promise of any benefit or bonus, whether in money or in kind, except when the intrinsic value of such an inducement is minimal;

(*f*) sponsorship of promotional meetings attended by persons qualified to prescribe or supply medicinal products;

(*g*) sponsorship of any scientific congress attended by persons qualified to prescribe or supply medicinal products and in particular where payment of their travelling and accommodation expenses is offered in connection therewith;

A response to a medicinal product which is **noxious** and **unintended**

- **Within** or **outside** the terms of the marketing authorisation.
- Outside → off label use, overdose, misuse, abuse, medication errors

Legislation Malta. Chapter 458 Medicines Act [Internet]. 2003; 1-51 [cited 2021 Feb 10]. Available from: https://legislation.mt/eli/cap/458/eng/pdf

8

Serious ADR - Definition

An ADR which results in:

- **Death**
- **Life threatening**
- **In-patient hospitalisation** or **prolongation of existing hospitalisation**
- Persistent or significant **disability** or **incapacity**
- **Congenital anomaly** or **birth defect**

European Commission. Directive 2001/83/EU of the European Parliament and of the Council on the Community code relating to medicinal products for human use [Internet]. Official Journal of The European Union. 2001; 2001L0083 [cited 2021 Feb 10]. Available from: https://www.ema.europa.eu/en/documents/regulatory-procedural-guideline/directive-2001/83/ec-european-parliament-council-6-november-2001-community-code-relating-medicinal-products-human-use_en.pdf

9

Spontaneous Reporting System

- Main system for identifying **previously undetected**, **uncommon** or **unexpected** ADRs
- Voluntary submission of ADR reports by both healthcare providers (HCPs) and patients
- Underreporting of ADRs: barrier for ADR monitoring

Ali MD, Hassan YA, Ahmad A, Alaqel O, Al-Harbi H, Al-Suhaimi NM. Knowledge, Practice and Attitudes Toward Pharmacovigilance and Adverse Drug Reactions Reporting Process Among Health Care Providers in Dammam, Saudi Arabia. Curr Drug Saf. 2018;13(1):21-25

Biagi C, Montanaro N, Buccellato E, Roberto G, Vaccheri A, Motola D. Underreporting in pharmacovigilance: an intervention for Italian GPs (Emilia–Romagna region). Eur J Clin Pharmacol. 2013;69(2):237–244

10

Spontaneous Reporting System

Statistics:

- Estimated that only **1–10%** of serious ADRs are reported

Klika C, Kaeding M, Schmälter J. The EU Pharmacovigilance System and Adverse Drug Reaction Reporting in Practice: A Critical Assessment. Eur. J. Risk Regul. Cambridge University Press; 2017;8(4):772–8

Table 1: Barriers towards ADR reporting (N=325)

Barriers	n	% of cases
Difficulty to understand whether an ADR has occurred or not	**154**	**47.4%**
ADR already well known and documented to occur	**133**	**40.9%**
Patient followed up by different professionals	**112**	**34.5%**
Lack of time	**98**	**30.2%**
Difficulty in accessing ADR reporting form	84	25.8%
Not knowing where to send the ADR reporting form	74	22.8%
Limited understanding of its value	55	16.9%
Concern that ADR reporting may generate extra work	33	10.2%
Not being aware that ADRs may be reported	34	10.5%
Lack of motivation	32	9.8%
Fear of consequences	27	8.3%
Other	28	8.6%

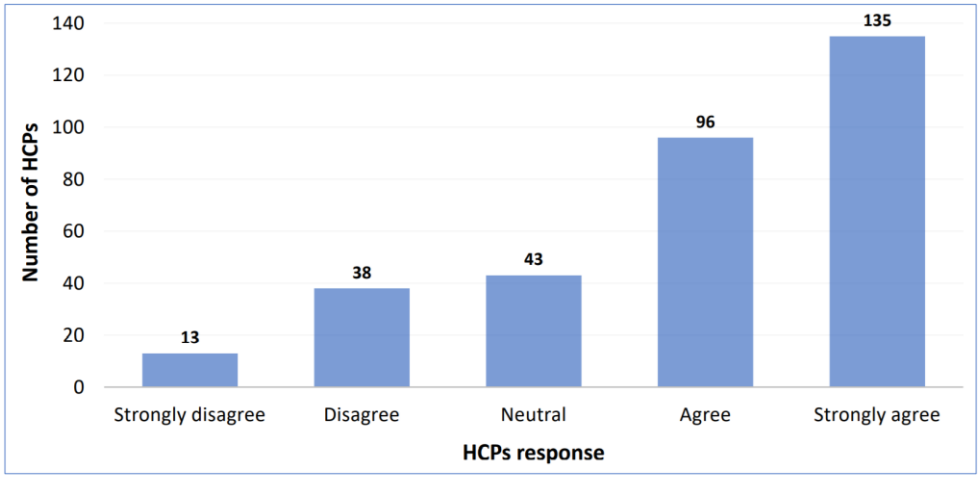
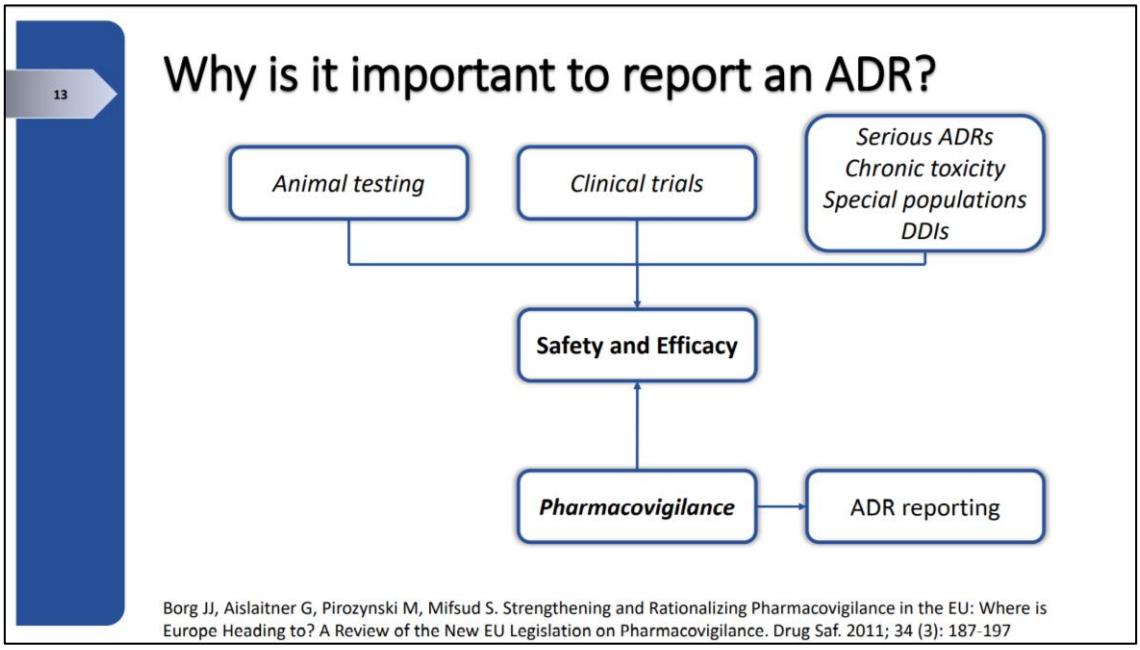


Figure 1. HCPs interest in receiving more education on ADR reporting (N=325)



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Spontaneous reporting of COVID-19 vaccination

- Vaccination campaign started on 27/12/2020
- **24 ADR reports** received:
  - **23** by HCPs and **1** by a patient
  - **5** marked as **serious ADRs:** 2 recovered, 2 in a recovery phase, 1 symptoms continuing

Spontaneous reporting of COVID-19 vaccination

The 24 ADR forms reported **69 adverse events** (AEs)

Table 2: Most common reported AEs

Reported Term	Number of AEs
Tiredness / drowsiness / lethargy / fatigue	8
Injection site pain	6
Fever	5
Facial paresthesia	4
Body aches/generalised pain/ pain in 4 limbs	3
Headache	3
Malaise	3

ADR reporting system

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ADR reporting

- Through detection of new ADRs, ADR reporting helps identify potential signals (serious events with very low frequency)
- Regulatory actions can be taken

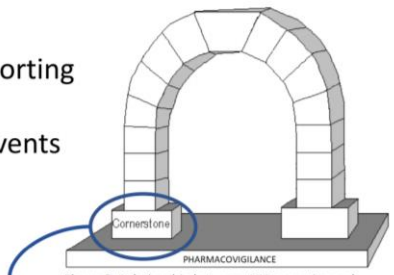

Figure 2. Relationship between ADR reporting and Pharmacovigilance

To report an ADR, it is not necessary to be certain of the causal relationship between the ADR and the medicinal product

Palleria C, Leporini C, Chimirri S, Marrazzo G, Sacchetta S, Bruno L, et al. Limitations and obstacles of the spontaneous adverse drugs reactions reporting: Two "challenging" case reports. J Pharmacol Pharmacother. 2013;4(Suppl 1):S66-72

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What to report? (1)

All suspected ADRs to all *medicines* (POM and OTC) and *vaccines*

All suspected ADRs in *special populations*

All suspected ADRs associated with *interactions*

Couper M. Safety of medicines - a guide to detecting and reporting adverse drug reaction - Why health professionals need to take action [Internet]. WHO; 2002 [Cited 2020 Sep 4]. Available from: http://www.digicollection.org/hss/en/d/Jh2992e/10.html

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What to report? (2)

Suspected ADRs associated with *drug withdrawals*

Suspected ADRs occurring from *overdose* or *medication error (ME)*

When there is a **lack of efficacy** or when suspected **pharmaceutical defects** are observed

Couper M. Safety of medicines - a guide to detecting and reporting adverse drug reaction - Why health professionals need to take action [Internet]. WHO; 2002 [Cited 2020 Sep 4]. Available from: http://www.digicollection.org/hss/en/d/Jh2992e/10.html

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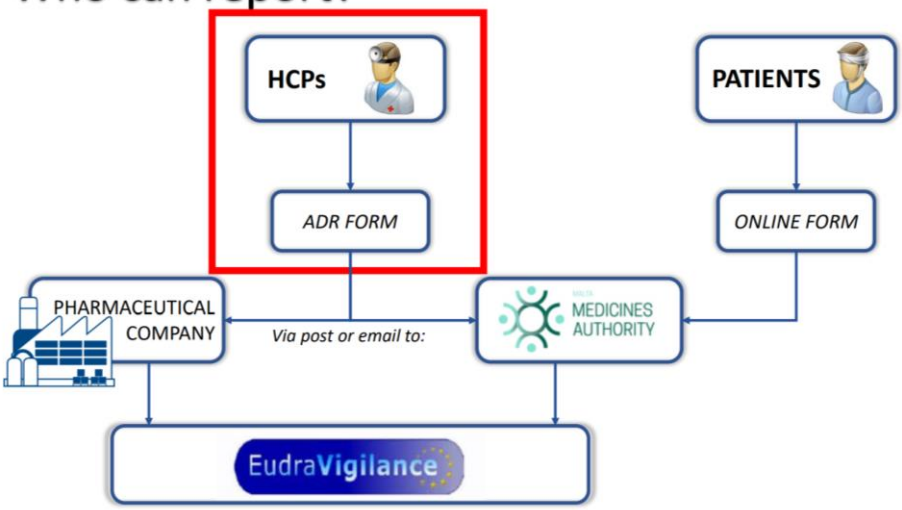
Who can report?



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Role of HCPs

- HCPs are critical in the success of ADR reporting system

"It shall be the duty of doctors and other healthcare professionals to immediately report to the Authority any suspected adverse reaction to a medicinal product in Malta"

Palleria C, Leporini C, Chimirri S, Marrazzo G, Sacchetta S, Bruno L, et al. Limitations and obstacles of the spontaneous adverse drugs reactions reporting: Two "challenging" case reports. J Pharmacol Pharmacother. 2013;4(Suppl 1):S66-72

Laws of Malta. SL 458.35 Pharmacovigilance Regulations, 2012. Government Gazette of Malta 2012; 18985:12399

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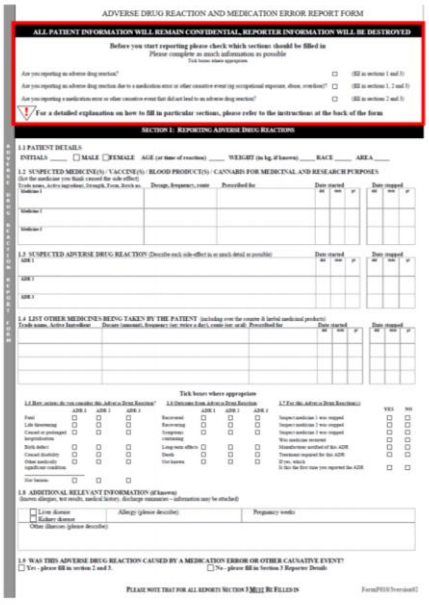
How to report?

- ADR reporting form which combines reporting of ADRs and medication errors

http://www.medicinesauthority.gov.mt/file.aspx?f=4496

Tanti A, Serracino-Inglott A, Borg JJ. Designing a national combined reporting form for adverse drug reactions and medication errors. East Mediterr Health J. 2015; 21(4):246-55

23

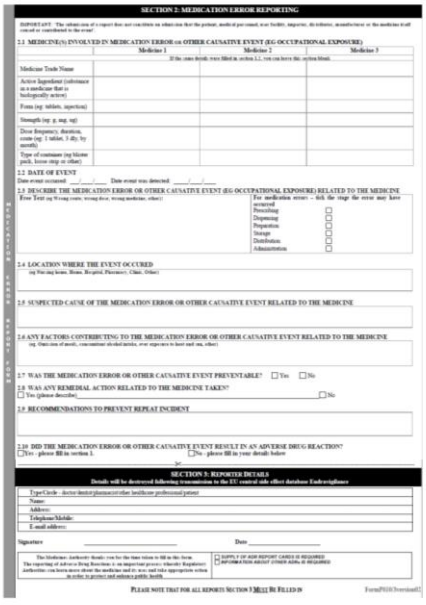

ADVERSE DRUG REACTION AND MEDICATION ERROR REPORT FORM

ALL PATIENT INFORMATION WILL REMAIN CONFIDENTIAL, REPORTER INFORMATION WILL BE DESTROYED

Before you start reporting please check which sections should be filled in
Please complete as much information as possible

For a detailed explanation on how to fill in particular sections, please refer to the instructions at the back of the form

SECTION 1: REPORTING ADVERSE DRUG REACTIONS


SECTION 2: MEDICATION ERROR REPORTING

SECTION 3: REPORTER DETAILS

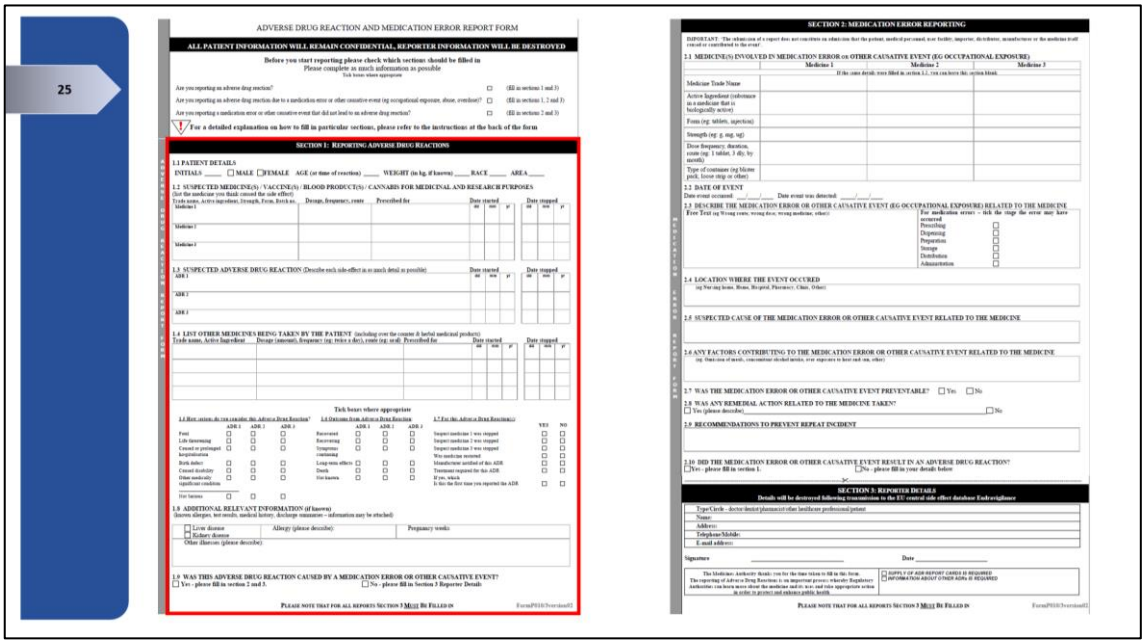
Decision tree

ALL PATIENT INFORMATION WILL REMAIN CONFIDENTIAL, REPORTER INFORMATION WILL BE DESTROYED

Before you start reporting please check which sections should be filled in
Please complete as much information as possible
Tick boxes where appropriate

Are you reporting an adverse drug reaction?	☐	(fill in sections 1 and 3)
Are you reporting an adverse drug reaction due to a medication error or other causative event (eg occupational exposure, abuse, overdose)?	☐	(fill in sections 1, 2 and 3)
Are you reporting a medication error or other causative event that did not lead to an adverse drug reaction?	☐	(fill in sections 2 and 3)

For a detailed explanation on how to fill in particular sections, please refer to the instructions at the back of the form



Section 1: Reporting ADRs

Minimum of **4** **criteria** for a valid ADR report

SECTION 1: REPORTING ADVERSE DRUG REACTIONS

1.1 PATIENT DETAILS

INITIALS **1** ☐ MALE ☐ FEMALE AGE (at time of reaction) ____ WEIGHT (in kg, if known) ____ RA

1.2 SUSPECTED MEDICINE(S) / VACCINE(S) / BLOOD PRODUCT(S) / CANNABIS FOR MEDICINAL AND RESEARCH PURPOSES
(list the medicine you think caused the side effect)

Trade name, Active ingredient, Strength, Form, Batch no.	Dosage, frequency, route	Prescribed for	Date started dd	Date started mm	Date started yr	Date stopped dd	Date stopped mm	Date stopped yr
Medicine 1 **2**								
Medicine 2								
Medicine 3								

1.3 SUSPECTED ADVERSE DRUG REACTION (Describe each side-effect in as much detail as possible)

	Date started dd	Date started mm	Date started yr	Date stopped dd	Date stopped mm	Date stopped yr
ADR 1 **3**						
ADR 2						
ADR 3						

Section 1: Reporting ADRs

1.4 LIST OTHER MEDICINES BEING TAKEN BY THE PATIENT (including over the counter & herbal medicinal products)

Trade name, Active Ingredient	Dosage (amount), frequency (eg: twice a day), route (eg: oral)	Prescribed for	Date started dd	Date started mm	Date started yr	Date stopped dd	Date stopped mm	Date stopped yr

Tick boxes where appropriate

1.5 How serious do you consider this Adverse Drug Reaction?

	ADR 1	ADR 2	ADR 3
Fatal	☐	☐	☐
Life threatening	☐	☐	☐
Caused or prolonged hospitalisation	☐	☐	☐
Birth defect	☐	☐	☐
Caused disability	☐	☐	☐
Other medically significant condition	☐	☐	☐
Not Serious	☐	☐	☐

1.6 Outcome from Adverse Drug Reaction:

	ADR 1	ADR 2	ADR 3
Recovered	☐	☐	☐
Recovering	☐	☐	☐
Symptoms continuing	☐	☐	☐
Long-term effects	☐	☐	☐
Death	☐	☐	☐
Not known	☐	☐	☐

1.7 For this Adverse Drug Reaction(s):

	YES	NO
Suspect medicine 1 was stopped	☐	☐
Suspect medicine 2 was stopped	☐	☐
Suspect medicine 3 was stopped	☐	☐
Was medicine restarted	☐	☐
Manufacturer notified of this ADR	☐	☐
Treatment required for this ADR	☐	☐
If yes, which Is this the first time you reported the ADR	☐	☐

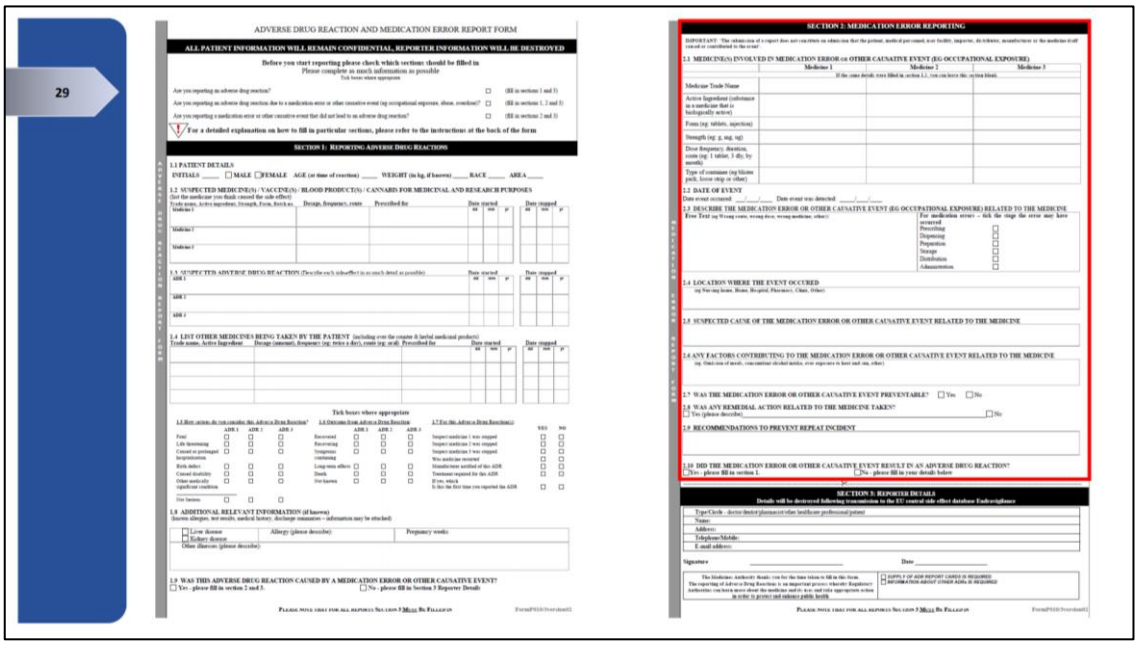
Section 1: Reporting ADRs

1.8 ADDITIONAL RELEVANT INFORMATION (if known)
(known allergies, test results, medical history, discharge summaries – information may be attached)

☐ Liver disease ☐ Kidney disease	Allergy (please describe):	Pregnancy weeks
Other illnesses (please describe):		

1.9 WAS THIS ADVERSE DRUG REACTION CAUSED BY A MEDICATION ERROR OR OTHER CAUSATIVE EVENT?
☐ **Yes - please fill in section 2 and 3.** ☐ **No - please fill in Section 3 Reporter Details**

PLEASE NOTE THAT FOR ALL REPORTS SECTION 3 MUST BE FILLED IN FormP010/3version02



Section 2: Medication Error Reporting

SECTION 2: MEDICATION ERROR REPORTING

IMPORTANT: 'The submission of a report does not constitute an admission that the patient, medical personnel, user facility, importer, distributor, manufacturer or the medicine itself caused or contributed to the event'.

2.1 MEDICINE(S) INVOLVED IN MEDICATION ERROR OR OTHER CAUSATIVE EVENT (EG OCCUPATIONAL EXPOSURE)

	Medicine 1	Medicine 2	Medicine 3
	If the same details were filled in section 1.2, you can leave this section blank		
Medicine Trade Name			
Active Ingredient (substance in a medicine that is biologically active)			
Form (eg: tablets, injection)			
Strength (eg: g, mg, ug)			
Dose frequency, duration, route (eg: 1 tablet, 3 dly, by mouth)			
Type of container (eg blister pack, loose strip or other)			

2.2 DATE OF EVENT

Date event occurred: ___/___/___ Date event was detected: ____/___/___

Section 2: Medication Error Reporting

2.3 DESCRIBE THE MEDICATION ERROR OR OTHER CAUSATIVE EVENT (EG OCCUPATIONAL EXPOSURE) RELATED TO THE MEDICINE

Free Text (eg Wrong route; wrong dose; wrong medicine; other):	**For medication errors – tick the stage the error may have occurred**
	Prescribing ☐ Dispensing ☐ Preparation ☐ Storage ☐ Distribution ☐ Administration ☐

2.4 LOCATION WHERE THE EVENT OCCURED

(eg Nursing home, Home, Hospital, Pharmacy, Clinic, Other)

2.5 SUSPECTED CAUSE OF THE MEDICATION ERROR OR OTHER CAUSATIVE EVENT RELATED TO THE MEDICINE

Section 2: Medication Error Reporting

2.6 ANY FACTORS CONTRIBUTING TO THE MEDICATION ERROR OR OTHER CAUSATIVE EVENT RELATED TO THE MEDICINE
(eg. Omission of meals, concomitant alcohol intake, over exposure to heat and sun, other)

2.7 WAS THE MEDICATION ERROR OR OTHER CAUSATIVE EVENT PREVENTABLE? ☐ Yes ☐ No

2.8 WAS ANY REMEDIAL ACTION RELATED TO THE MEDICINE TAKEN?
☐ Yes (please describe)_____ ☐ No

2.9 RECOMMENDATIONS TO PREVENT REPEAT INCIDENT

2.10 DID THE MEDICATION ERROR OR OTHER CAUSATIVE EVENT RESULT IN AN ADVERSE DRUG REACTION?
☐**Yes - please fill in section 1.** ☐**No - please fill in your details below**

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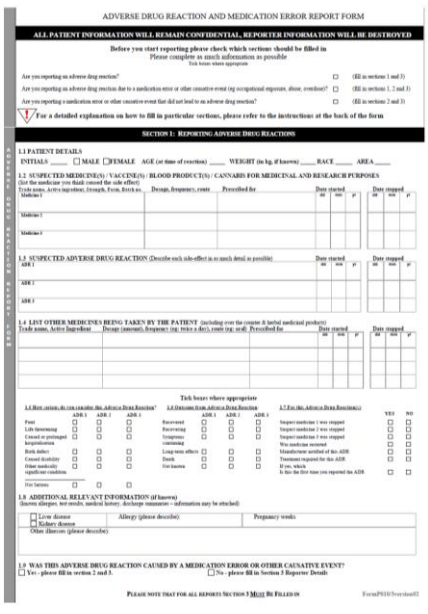
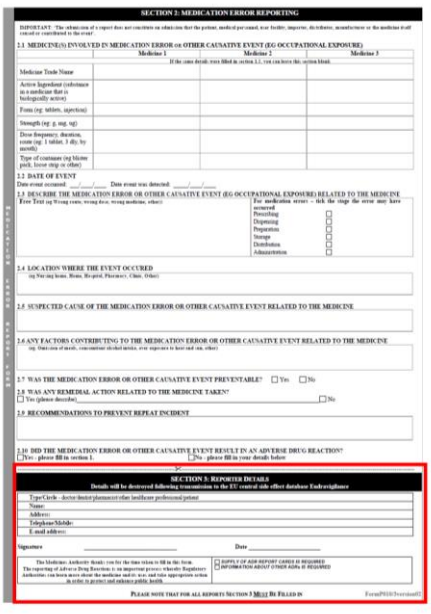

ADVERSE DRUG REACTION AND MEDICATION ERROR REPORT FORM

ALL PATIENT INFORMATION WILL REMAIN CONFIDENTIAL, REPORTER INFORMATION WILL BE DESTROYED

SECTION 1: REPORTING ADVERSE DRUG REACTIONS


SECTION 2: MEDICATION ERROR REPORTING

SECTION 3: REPORTER DETAILS

Section 3: Reporter Details

SECTION 3: REPORTER DETAILS
Details will be destroyed following transmission to the EU central side effect database Eudravigilance

4	Type/Circle - doctor/dentist/pharmacist/other healthcare professional/patient
Name:	Elisa Curtolo
Address:	Triq it-Torri, Msida, Malta
Telephone/Mobile:	123456789
E-mail address:	elisa.curtolo.18@um.edu.mt

Signature _____ Date 22/02/2021

The Medicines Authority thanks you for the time taken to fill in this form. The reporting of Adverse Drug Reactions is an important process whereby Regulatory Authorities can learn more about the medicine and its uses and take appropriate action in order to protect and enhance public health	☐ *SUPPLY OF ADR REPORT CARDS IS REQUIRED* ☐ *INFORMATION ABOUT OTHER ADRs IS REQUIRED*

PLEASE NOTE THAT FOR ALL REPORTS SECTION 3 MUST BE FILLED IN FormP010/3version02

SECTION 3 MUST BE FILLED IN FOR ALL REPORTS

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How to fill in the ADR reporting form?

1) Identifiable patient
2) Suspected medicinal product
3) Suspected ADR
4) Identifiable reporter

DATES: "dd/mm/yyyy"

Details which facilitate evaluation:

- ADR start/stop date
- Suspect drug start/stop date
- Indication of the suspected drug
- Patient outcome and seriousness
- Rechallenge and Dechallenge
- Patient details
  - Past medical history
  - Concomitant drugs
- Laboratory data

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Quality of reports

Good quality of Data → Better Causality Assessment → Appropriate and timely regulatory action

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Where to send the ADR reporting form?

BY POST TO

Malta Medicines Authority
Sir Temi Żammit Buildings,
Malta Life Sciences Park,
San Ġwann SĠN 3000
Malta

OR

BY EMAIL TO

postlicensing.medicinesauthority@gov.mt

OR

BY POST OR EMAIL TO

the Marketing Authorisation Holder of that product

Details may be found on the PIL inside every box

Do not send the same report to both the Malta Medicines Authority (MMA) and to the Marketing Authorisation Holder (MAH)

Case studies

Example 1

A 33-year-old female patient was administered Cominarty (batch no EJ6796) on 30/12/2020. Within 10 minutes from administration, patient developed an allergic reaction, her blood pressure increased and she also developed a rash in the upper chest and neck.

From follow-up information received on 05/01/2021, it emerged that patient fully recovered from the event after few hours and was discharged from the Accident and Emergency ward.

Decision tree

ALL PATIENT INFORMATION WILL REMAIN CONFIDENTIAL, REPORTER INFORMATION WILL BE DESTROYED

Before you start reporting please check which sections should be filled in
Please complete as much information as possible
Tick boxes where appropriate

Are you reporting an adverse drug reaction?	☒	(fill in sections 1 and 3)
Are you reporting an adverse drug reaction due to a medication error or other causative event (eg occupational exposure, abuse, overdose)?	☐	(fill in sections 1, 2 and 3)
Are you reporting a medication error or other causative event that did not lead to an adverse drug reaction?	☐	(fill in sections 2 and 3)

For a detailed explanation on how to fill in particular sections, please refer to the instructions at the back of the form

Section 1: Reporting ADRs

SECTION 1: REPORTING ADVERSE DRUG REACTIONS

1.1 PATIENT DETAILS

INITIALS _____ ☐ MALE ☒ FEMALE AGE (at time of reaction) 33 WEIGHT (in kg, if known) _____ RACE _____ AREA _____

1.2 SUSPECTED MEDICINE(S) / VACCINE(S) / BLOOD PRODUCT(S) / CANNABIS FOR MEDICINAL AND RESEARCH PURPOSES
(list the medicine you think caused the side effect)

Trade name, Active ingredient, Strength, Form, Batch no.	Dosage, frequency, route	Prescribed for	Date started dd	mm	yr	Date stopped dd	mm	yr
Medicine 1 Cominarty (batch no EJ6796)			30	12	2020			
Medicine 2								
Medicine 3								

1.3 SUSPECTED ADVERSE DRUG REACTION (Describe each side-effect in as much detail as possible)

	Date started dd	mm	yr	Date stopped dd	mm	yr
ADR 1 Allergic reaction	30	12	2020			
ADR 2 Persistently high blood pressure	30	12	2020			
ADR 3 Rash in the upper chest and neck	30	12	2020			

Section 1: Reporting ADRs

1.4 LIST OTHER MEDICINES BEING TAKEN BY THE PATIENT (including over the counter & herbal medicinal products)

Trade name, Active Ingredient	Dosage (amount), frequency (eg: twice a day), route (eg: oral)	Prescribed for	Date started dd	Date started mm	Date started yr	Date stopped dd	Date stopped mm	Date stopped yr

Tick boxes where appropriate

1.5 How serious do you consider this Adverse Drug Reaction?

	ADR 1	ADR 2	ADR 3
Fatal	☐	☐	☐
Life threatening	☐	☐	☐
Caused or prolonged hospitalisation	☐	☐	☐
Birth defect	☐	☐	☐
Caused disability	☐	☐	☐
Other medically significant condition	☒	☒	☒
Not Serious	☐	☐	☐

1.6 Outcome from Adverse Drug Reaction:

	ADR 1	ADR 2	ADR 3
Recovered	☐	☐	☐
Recovering	☐	☐	☐
Symptoms continuing	☐	☐	☐
Long-term effects	☐	☐	☐
Death	☐	☐	☐
Not known	☒	☒	☒

1.7 For this Adverse Drug Reaction(s):

	YES	NO
Suspect medicine 1 was stopped	☐	☐
Suspect medicine 2 was stopped	☐	☐
Suspect medicine 3 was stopped	☐	☐
Was medicine restarted	☐	☐
Manufacturer notified of this ADR	☐	☐
Treatment required for this ADR	☒	☐
If yes, which Is this the first time you reported the ADR	☒	☐

Section 1: Reporting ADRs

1.8 ADDITIONAL RELEVANT INFORMATION (if known)
(known allergies, test results, medical history, discharge summaries – information may be attached)

☐ Liver disease ☐ Kidney disease	Allergy (please describe): **Penicillin and nuts**	Pregnancy weeks
Other illnesses (please describe): **Hypertensive**		

1.9 WAS THIS ADVERSE DRUG REACTION CAUSED BY A MEDICATION ERROR OR OTHER CAUSATIVE EVENT?

☐ **Yes - please fill in section 2 and 3.** ☒ **No - please fill in Section 3 Reporter Details**

PLEASE NOTE THAT FOR ALL REPORTS SECTION 3 MUST BE FILLED IN

FormP010/3version02

Section 2: Medication Error Reporting

In this case not applicable

SECTION 2: MEDICATION ERROR REPORTING

IMPORTANT: 'The submission of a report does not constitute an admission that the patient, medical personnel, user facility, importer, distributor, manufacturer or the medicine itself caused or contributed to the event'.

2.1 MEDICINE(S) INVOLVED IN MEDICATION ERROR OR OTHER CAUSATIVE EVENT (EG OCCUPATIONAL EXPOSURE)

	Medicine 1	Medicine 2	Medicine 3
	If the same details were filled in section 1.2, you can leave this section blank		
Medicine Trade Name			
Active Ingredient (substance in a medicine that is biologically active)			
Form (eg: tablets, injection)			
Strength (eg: g, mg, ug)			
Dose frequency, duration, route (eg: 1 tablet, 3 dly, by mouth)			
Type of container (eg blister pack, loose strip or other)			

2.2 DATE OF EVENT

Date event occurred: __/____/____ Date event was detected: _____/____/____

Section 3: Reporter Details

SECTION 3: REPORTER DETAILS

Details will be destroyed following transmission to the EU central side effect database Eudravigilance

Type/Circle - doctor/dentist/pharmacist/other healthcare professional/patient	
Name:	Elisa Curtolo
Address:	Triq it-Torri, Msida, Malta
Telephone/Mobile:	123456789
E-mail address:	elisa.curtolo.18@um.edu.mt

Signature _____ **Date** 30/12/2020

The Medicines Authority thanks you for the time taken to fill in this form. The reporting of Adverse Drug Reactions is an important process whereby Regulatory Authorities can learn more about the medicine and its uses and take appropriate action in order to protect and enhance public health	☐ *SUPPLY OF ADR REPORT CARDS IS REQUIRED* ☐ *INFORMATION ABOUT OTHER ADRs IS REQUIRED*

PLEASE NOTE THAT FOR ALL REPORTS SECTION 3 MUST BE FILLED IN

FormP010/3version02

SECTION 3 MUST BE FILLED IN FOR ALL REPORTS

Example 2

MV is a 52-year-old Caucasian man who was prescribed Metformin Hydrochloride tablets 500mg for diabetes type II, to be taken as one tablet twice a day by mouth. MV weighs 95Kg. He starts the metformin treatment on 15th February 2020 in the morning. The next day, after taking his evening dose of metformin, Mr MV felt nausea and he vomited only once. He also had diarrhoea at around 9pm. The next morning, he contacted his doctor who advised him to continue with the treatment and reminded Mr MV to take his tablets with food.

Mr MV had episodes of diarrhoea for the next 4 days, on the fifth day (20th February 2020) he felt better and the diarrhoea stopped.

Mr MV takes also two tablets of paracetamol 500 mg TDS/PRN by mouth for his back pain. He started paracetamol 4 months earlier (20th November 2019). He has no known allergies and the ADR was not due to a medication error.

Decision tree

ALL PATIENT INFORMATION WILL REMAIN CONFIDENTIAL, REPORTER INFORMATION WILL BE DESTROYED

Before you start reporting please check which sections should be filled in

Please complete as much information as possible

Tick boxes where appropriate

Are you reporting an adverse drug reaction?	☒	(fill in sections 1 and 3)
Are you reporting an adverse drug reaction due to a medication error or other causative event (eg occupational exposure, abuse, overdose)?	☐	(fill in sections 1, 2 and 3)
Are you reporting a medication error or other causative event that did not lead to an adverse drug reaction?	☐	(fill in sections 2 and 3)

For a detailed explanation on how to fill in particular sections, please refer to the instructions at the back of the form

Section 1: Reporting ADRs

SECTION 1: REPORTING ADVERSE DRUG REACTIONS

1.1 PATIENT DETAILS

INITIALS MV [X] MALE [ ] FEMALE AGE (at time of reaction) 52 WEIGHT (in kg, if known) 95 RACE Caucasian AREA ____

1.2 SUSPECTED MEDICINE(S) / VACCINE(S) / BLOOD PRODUCT(S) / CANNABIS FOR MEDICINAL AND RESEARCH PURPOSES
(list the medicine you think caused the side effect)

Trade name, Active ingredient, Strength, Form, Batch no.	Dosage, frequency, route	Prescribed for	Date started (dd mm yr)	Date stopped (dd mm yr)
Medicine 1 Metformin Hydrochloride 500mg tablet	500 mg BD by mouth	Type 2 diabetes	15/02/2020	Ongoing
Medicine 2				
Medicine 3				

1.3 SUSPECTED ADVERSE DRUG REACTION (Describe each side-effect in as much detail as possible)

	Date started (dd mm yr)	Date stopped (dd mm yr)
ADR 1 Nausea	16/02/2020	16/02/2020
ADR 2 Vomiting	16/02/2020	16/02/2020
ADR 3 Diarrhoea	16/02/2020	20/02/2020

Section 1: Reporting ADRs

1.4 LIST OTHER MEDICINES BEING TAKEN BY THE PATIENT (including over the counter & herbal medicinal products)

Trade name, Active Ingredient	Dosage (amount), frequency (eg: twice a day), route (eg: oral)	Prescribed for	Date started (dd mm yr)	Date stopped (dd mm yr)
Paracetamol 500mg tablets	Two 500mg tablets TDS/PRN by mouth	Back pain	20/11/2019	Ongoing

Tick boxes where appropriate

1.5 How serious do you consider this Adverse Drug Reaction?

	ADR 1	ADR 2	ADR 3
Fatal	☐	☐	☐
Life threatening	☐	☐	☐
Caused or prolonged hospitalisation	☐	☐	☐
Birth defect	☐	☐	☐
Caused disability	☐	☐	☐
Other medically significant condition	☐	☐	☐
Not Serious	☒	☒	☒

1.6 Outcome from Adverse Drug Reaction:

	ADR 1	ADR 2	ADR 3
Recovered	☒	☒	☒
Recovering	☐	☐	☐
Symptoms continuing	☐	☐	☐
Long-term effects	☐	☐	☐
Death	☐	☐	☐
Not known	☐	☐	☐

1.7 For this Adverse Drug Reaction(s):

	YES	NO
Suspect medicine 1 was stopped	☐	☒
Suspect medicine 2 was stopped	☐	☐
Suspect medicine 3 was stopped	☐	☐
Was medicine restarted	☐	☐
Manufacturer notified of this ADR	☐	☐
Treatment required for this ADR	☐	☒
If yes, which Is this the first time you reported the ADR	☐	☒

Section 1: Reporting ADRs

1.8 ADDITIONAL RELEVANT INFORMATION (if known)
(known allergies, test results, medical history, discharge summaries – information may be attached)

☐ Liver disease ☐ Kidney disease	Allergy (please describe): NONE	Pregnancy weeks
Other illnesses (please describe):		

1.9 WAS THIS ADVERSE DRUG REACTION CAUSED BY A MEDICATION ERROR OR OTHER CAUSATIVE EVENT?
☐ **Yes - please fill in section 2 and 3.** ☒ **No - please fill in Section 3 Reporter Details**

PLEASE NOTE THAT FOR ALL REPORTS SECTION 3 MUST BE FILLED IN FormP010/3version02

Section 2: Medication Error Reporting

In this case not applicable

SECTION 2: MEDICATION ERROR REPORTING

IMPORTANT: 'The submission of a report does not constitute an admission that the patient, medical personnel, user facility, importer, distributor, manufacturer or the medicine itself caused or contributed to the event'.

2.1 MEDICINE(S) INVOLVED IN MEDICATION ERROR OR OTHER CAUSATIVE EVENT (EG OCCUPATIONAL EXPOSURE)

	Medicine 1	Medicine 2	Medicine 3
If the same details were filled in section 1.2, you can leave this section blank			
Medicine Trade Name			
Active Ingredient (substance in a medicine that is biologically active)			
Form (eg: tablets, injection)			
Strength (eg: g, mg, ug)			
Dose frequency, duration, route (eg: 1 tablet, 3 dly, by mouth)			
Type of container (eg blister pack, loose strip or other)			

2.2 DATE OF EVENT
Date event occurred: __/___/____ Date event was detected: ____/___/____

Section 3: Reporter Details

SECTION 3: REPORTER DETAILS
Details will be destroyed following transmission to the EU central side effect database Eudravigilance

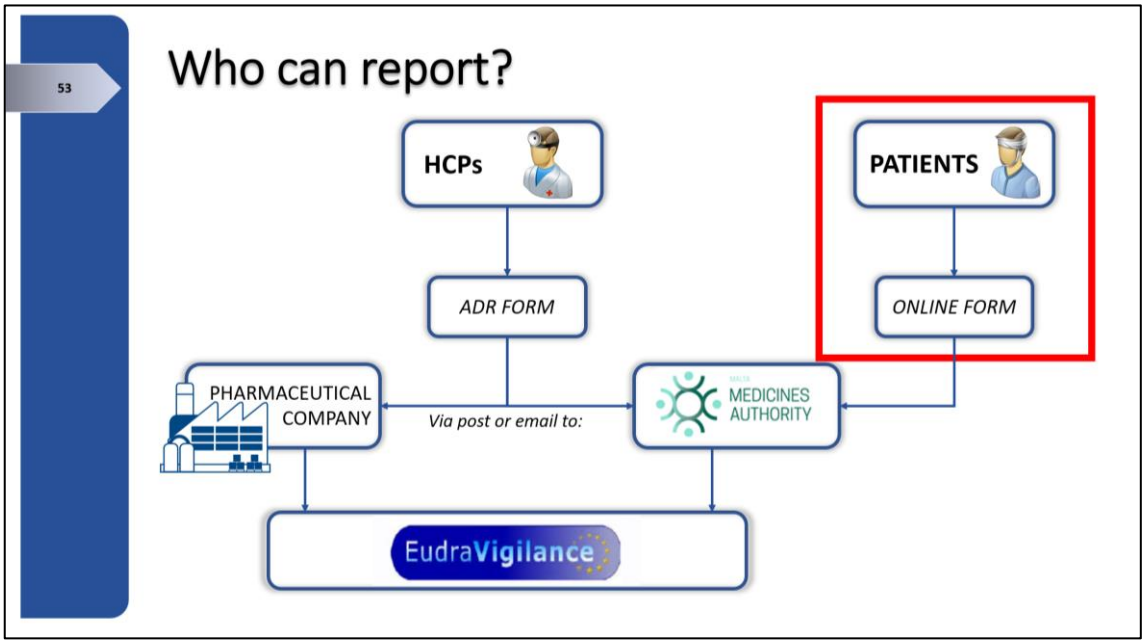
Type/Circle - doctor/dentist/pharmacist/other healthcare professional/patient	
Name:	Elisa Curtolo
Address:	Triq it-Torri, Msida, Malta
Telephone/Mobile:	123456789
E-mail address:	elisa.curtolo.18@um.edu.mt

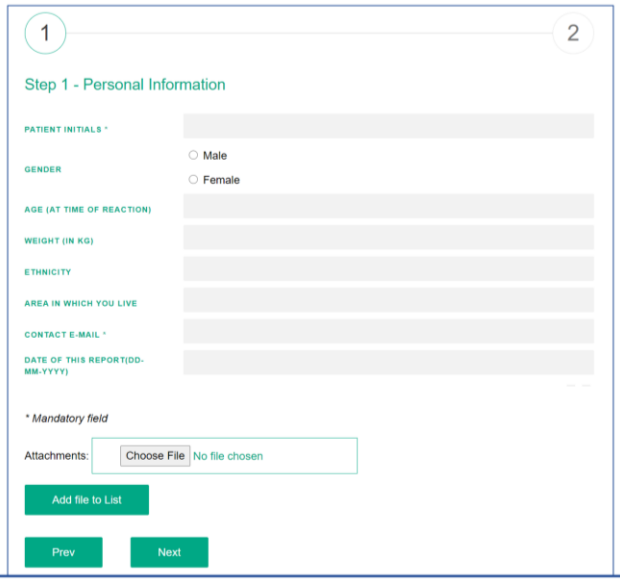
Signature _____ Date 22/02/2021

The Medicines Authority thanks you for the time taken to fill in this form. The reporting of Adverse Drug Reactions is an important process whereby Regulatory Authorities can learn more about the medicine and its uses and take appropriate action in order to protect and enhance public health	☐ *SUPPLY OF ADR REPORT CARDS IS REQUIRED* ☐ *INFORMATION ABOUT OTHER ADRs IS REQUIRED*

PLEASE NOTE THAT FOR ALL REPORTS SECTION 3 MUST BE FILLED IN FormP010/3version02

SECTION 3 MUST BE FILLED IN FOR ALL REPORTS





http://www.medicinesauthority.gov.mt/form-details?surID=35&cat=3

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Key-points

- Pharmacovigilance promotes appropriate use of medicines, monitors ADRs and enhances patient safety
- All suspected ADRs to all medicines and vaccines have to be reported
- All HCPs are crucial in reporting an ADR
- 4 minimum criteria for the validity of an ADR report:
  1. An identifiable reporter (e.g. doctor, pharmacist, dentist, nurse)
  2. An identifiable patient (initials or age or date of birth or sex)
  3. A suspected medicinal product
  4. A suspected ADR
- Sections to fill:
  - Section 1 and Section 3 when reporting an ADR
  - Section 1, Section 2 and Section 3 when reporting an ADR due to ME
  - Section 2 and Section 3 when reporting a ME
- The ADR reporting form can be sent either to the MMA or the MAH

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Useful links

- Malta Medicines Authority: http://www.medicinesauthority.gov.mt/
- ADR reporting form for **HCPs:** http://www.medicinesauthority.gov.mt/file.aspx?f=4496
- ADR reporting form for **patients:** http://www.medicinesauthority.gov.mt/form-details?surID=35&cat=3

L-Università ta' Malta

Thank you for your participation

Evaluation form (link): https://docs.google.com/forms/d/e/1FAIpQLScDSnaJBLxO5aDKx30TJkSmWZpFa4anyeaBok7H7fw_pWSxcA/viewform?usp=sf_link

Elisa Curtolo

elisa.curtolo.18@um.edu.mt

Pharmacovigilance in the time of a pandemic crisis – Adverse Drug Reaction reporting – Part 2: Outcomes

Elisa Curtolo
Doctorate in Pharmacy candidate
March 2021

Salient points of the 1st webinar

- Pharmacovigilance promotes appropriate use of medicines, monitors adverse drug reactions (ADRs) and enhances patient safety
- All suspected ADRs to all medicines and vaccines have to be reported
- All healthcare professionals (HCPs) are crucial in reporting an ADR

http://www.medicinesauthority.gov.mt/file.aspx?f=4496

4

Salient points of the 1st webinar

- 4 minimum criteria for the validity of an ADR report:
  1. An identifiable **reporter** (profession, name, contact details)
  2. An identifiable **patient** (initials or age or date of birth or sex)
  3. A suspected **medicinal product** (brand name and batch n° for vaccines)
  4. A suspected **ADR**
- The ADR reporting form can be sent either to the Malta Medicines Authority (MMA) or to the Marketing Authorisation Holder (MAH)

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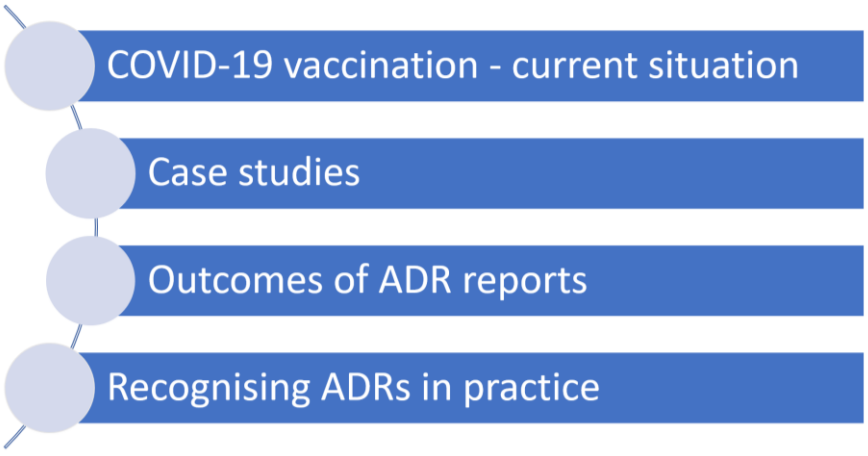
Overview



COVID-19 vaccination – current situation

Covid-19 vaccine Pfizer-Biontech – ADR reports

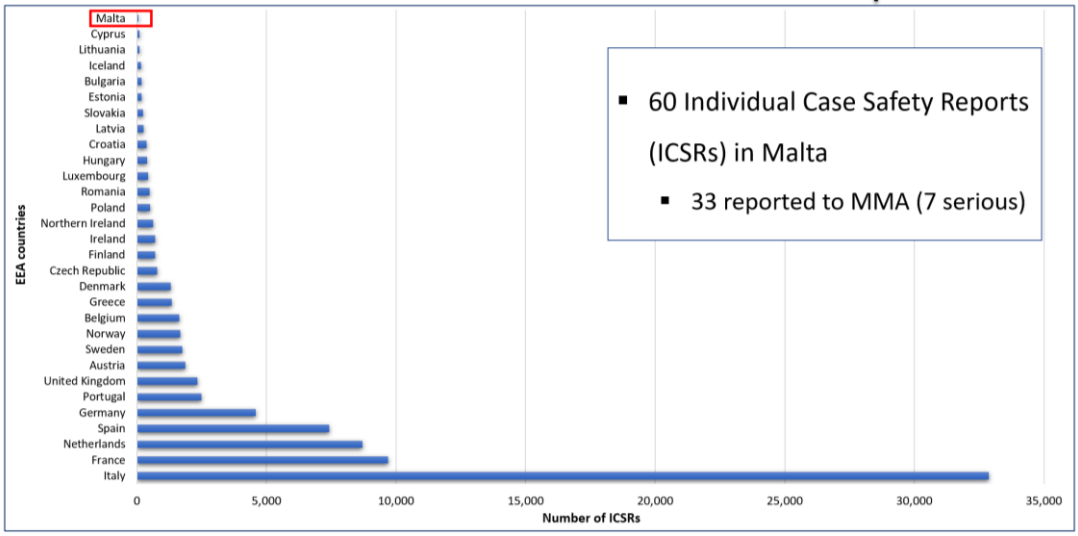


Figure 1: *Number of ICSRs in EEA countries for* ***Comirnaty*** *(TOZINAMERAN) (N= 102,100)*

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Covid-19 vaccine Pfizer-Biontech – ADR reports per reaction group

Table 1: *Number of ICSRs by reaction group for* ***Comirnaty*** *(TOZINAMERAN) (N= 102,100)*

Reaction group	N of ICSRs – Serious	N of ICSRs – Non serious
Gastrointestinal disorders	8,062	15,012
General disorders and administration site conditions	18,480	53,592
Musculoskeletal and connective tissue disorders	8,816	28,549
Nervous system disorders	14,472	30,521

Covid-19 vaccine Pfizer-Biontech – ADR outcomes

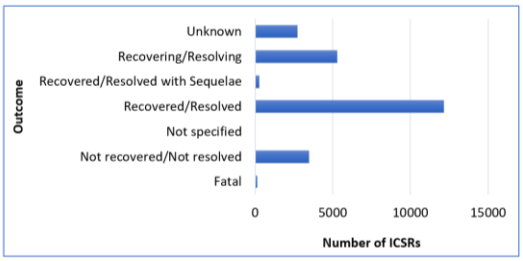

Figure 2: *Outcome of Gastrointestinal disorders (n=23,074)*

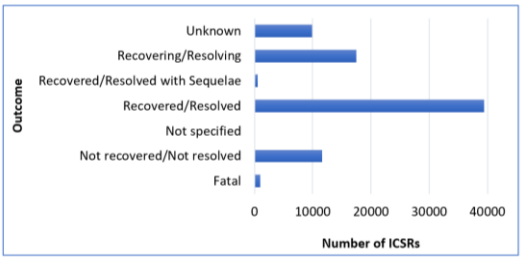

Figure 3: *Outcome General disorders and administration site conditions (n=72,072)*

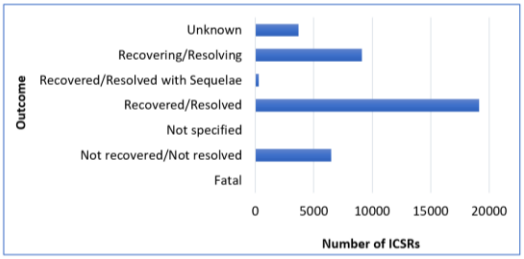

Figure 4: *Outcome Musculoskeletal and connective tissue disorders (n=37,365)*

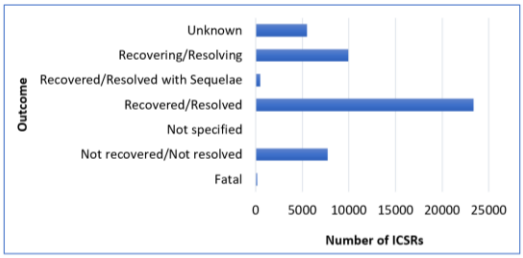

Figure 5: *Outcome of Nervous system disorders (n=44,993)*

Covid-19 vaccine ASTRAZENECA – ADR reports

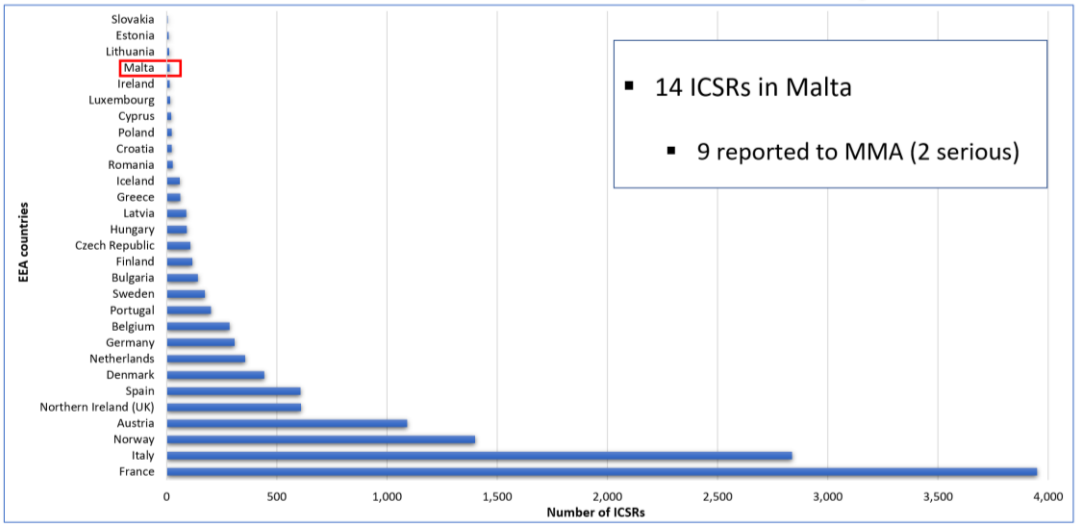

Figure 6: *Number of ICSRs in EEA countries for* ***CHADOX1 NCOV-19*** *(N= 54,571)*

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Covid-19 vaccine ASTRAZENECA – ADR reports per reaction group

Table 2: *Number of ICSRs by reaction group for* ***CHADOX1 NCOV-19*** *(N= 54,571)*

Reaction group	N of ICSRs – Serious	N of ICSRs – Non serious
Gastrointestinal disorders	13,443	4,048
General disorders and administration site conditions	29,146	13,221
Musculoskeletal and connective tissue disorders	14,315	8,543
Nervous system disorders	24,156	8,334

Covid-19 vaccine ASTRAZENECA – ADR outcomes

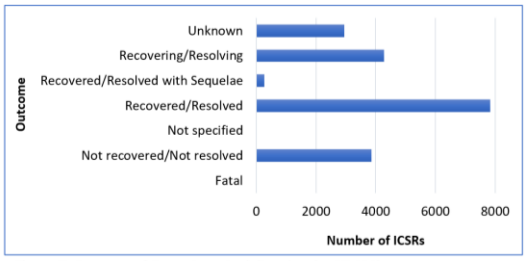

Figure 7: *Outcome of Gastrointestinal disorders (n=17,491)*

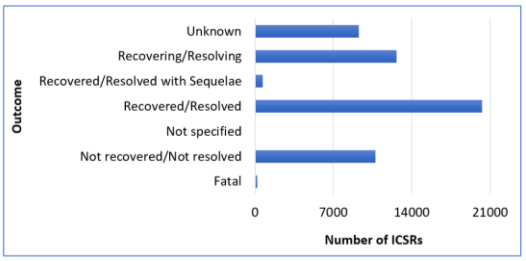

Figure 8: *Outcome General disorders and administration site conditions (n=42,367)*

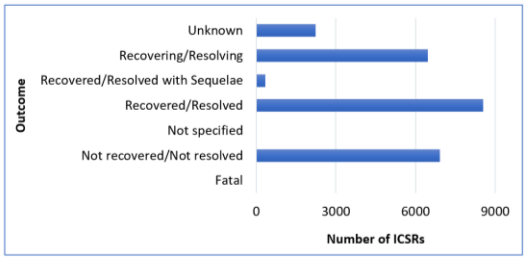

Figure 9: *Outcome Musculoskeletal and connective tissue disorders (n=22,858)*

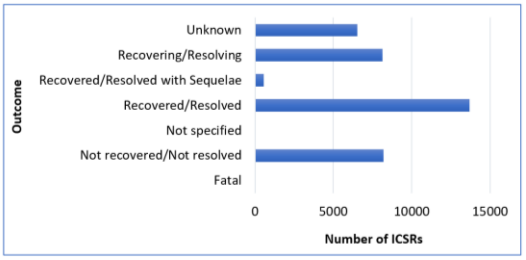

Figure 10: *Outcome of Nervous system disorders (n=32,490)*

Covid-19 vaccine MODERNA – ADR reports

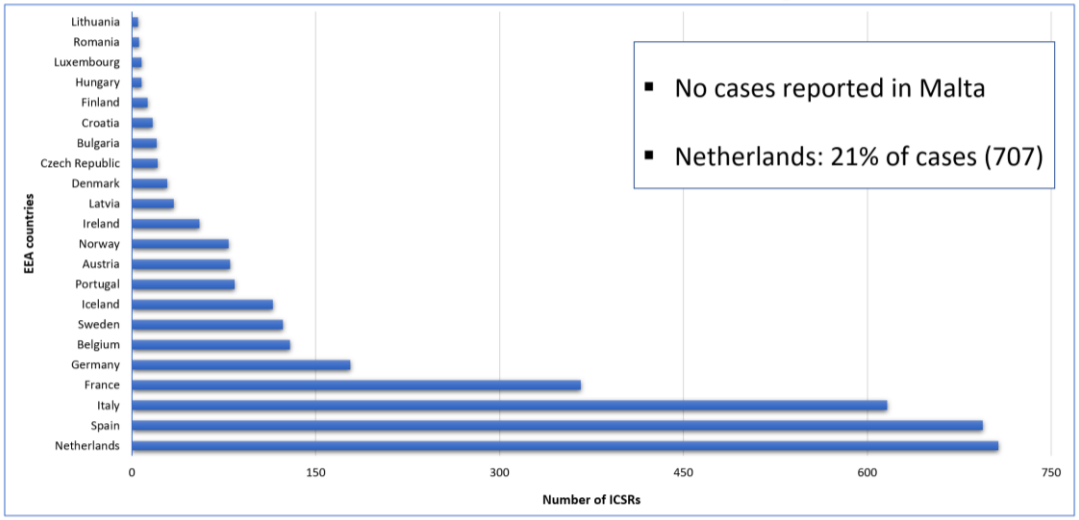

Figure 11: *Number of ICSRs in EEA countries for* ***CX-024414*** *(N=5,939)*

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Covid-19 vaccine MODERNA – ADR reports per reaction group

Table 3: *Number of ICSRs by reaction group for* ***CX-024414*** *(N=5,939)*

Reaction group	N of ICSRs – Serious	N of ICSRs – Non serious
Gastrointestinal disorders	704	579
General disorders and administration site conditions	1,737	2,461
Musculoskeletal and connective tissue disorders	604	1,123
Nervous system disorders	1,318	1,006

Covid-19 vaccine MODERNA – ADR outcomes

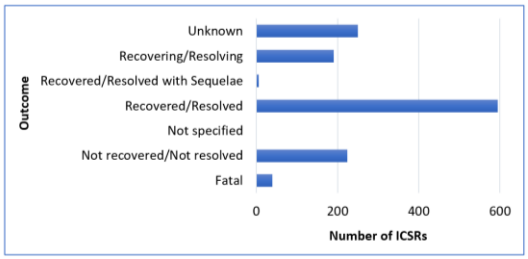


Figure 12: *Outcome of Gastrointestinal disorders (n=1,283)*

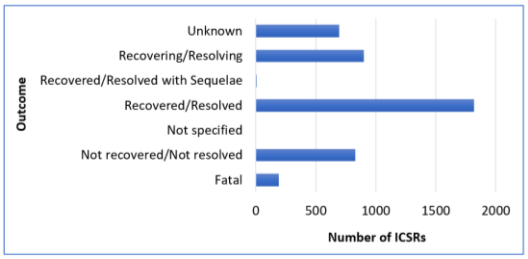


Figure 13: *Outcome General disorders and administration site conditions (n=4,198)*

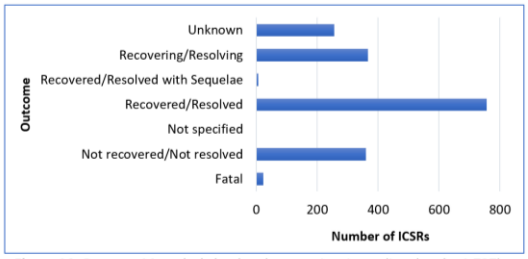


Figure 14: *Outcome Musculoskeletal and connective tissue disorders (n=1,727)*

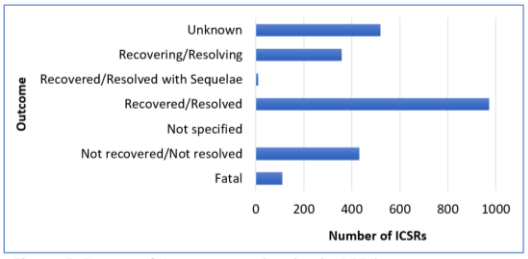


Figure 15: *Outcome of Nervous system disorders (n=2,324)*

Case studies

Example 1

A 40-year-old female patient was administered COMIRNATY - TOZINAMERAN 0.3mL (batch no XXXXX) on 21/02/2021. Within 10 minutes from administration, the patient experienced tachycardia and sternal pain. The patient was kept under observation and then discharged. The patient was not taking any concomitant medications and did not suffer from any allergies.

Decision tree

ALL PATIENT INFORMATION WILL REMAIN CONFIDENTIAL, REPORTER INFORMATION WILL BE DESTROYED

Before you start reporting please check which sections should be filled in
Please complete as much information as possible
Tick boxes where appropriate

Are you reporting an adverse drug reaction?	☒	(fill in sections 1 and 3)
Are you reporting an adverse drug reaction due to a medication error or other causative event (eg occupational exposure, abuse, overdose)?	☐	(fill in sections 1, 2 and 3)
Are you reporting a medication error or other causative event that did not lead to an adverse drug reaction?	☐	(fill in sections 2 and 3)

For a detailed explanation on how to fill in particular sections, please refer to the instructions at the back of the form

Section 1: Reporting ADRs

SECTION 1: REPORTING ADVERSE DRUG REACTIONS

1.1 PATIENT DETAILS

INITIALS _____ ☐ MALE ☒ FEMALE AGE (at time of reaction) 40 WEIGHT (in kg, if known) _____ RACE _____ AREA _____

1.2 SUSPECTED MEDICINE(S) / VACCINE(S) / BLOOD PRODUCT(S) / CANNABIS FOR MEDICINAL AND RESEARCH PURPOSES
(list the medicine you think caused the side effect)

Trade name, Active ingredient, Strength, Form, Batch no.	Dosage, frequency, route	Prescribed for	Date started (dd mm yr)	Date stopped (dd mm yr)
Medicine 1: Comirnaty (batch no XXXXX)	0.3 mL IM	COVID-19 immunisation	21/02/2021	
Medicine 2				
Medicine 3				

1.3 SUSPECTED ADVERSE DRUG REACTION (Describe each side-effect in as much detail as possible)

	Date started (dd mm yr)	Date stopped (dd mm yr)
ADR 1: Tachycardia	21/02/2021	21/02/2021
ADR 2: Sternal pain	21/02/2021	21/02/2021
ADR 3		

Section 1: Reporting ADRs

1.4 LIST OTHER MEDICINES BEING TAKEN BY THE PATIENT (including over the counter & herbal medicinal products)

Trade name, Active Ingredient	Dosage (amount), frequency (eg: twice a day), route (eg: oral)	Prescribed for	Date started dd	Date started mm	Date started yr	Date stopped dd	Date stopped mm	Date stopped yr
NONE								

Tick boxes where appropriate

1.5 How serious do you consider this Adverse Drug Reaction?

	ADR 1	ADR 2	ADR 3
Fatal	☐	☐	☐
Life threatening	☐	☐	☐
Caused or prolonged hospitalisation	☐	☐	☐
Birth defect	☐	☐	☐
Caused disability	☐	☐	☐
Other medically significant condition	☒	☒	☐
Not Serious	☐	☐	☐

1.6 Outcome from Adverse Drug Reaction:

	ADR 1	ADR 2	ADR 3
Recovered	☒	☒	☐
Recovering	☐	☐	☐
Symptoms continuing	☐	☐	☐
Long-term effects	☐	☐	☐
Death	☐	☐	☐
Not known	☐	☐	☐

1.7 For this Adverse Drug Reaction(s):

	YES	NO
Suspect medicine 1 was stopped	☐	☐
Suspect medicine 2 was stopped	☐	☐
Suspect medicine 3 was stopped	☐	☐
Was medicine restarted	☐	☐
Manufacturer notified of this ADR	☐	☐
Treatment required for this ADR	☐	☒
If yes, which Is this the first time you reported the ADR	☒	☐

Section 1: Reporting ADRs

1.8 ADDITIONAL RELEVANT INFORMATION (if known)
(known allergies, test results, medical history, discharge summaries – information may be attached)

☐ Liver disease ☐ Kidney disease	Allergy (please describe): NONE	Pregnancy weeks
Other illnesses (please describe):		

1.9 WAS THIS ADVERSE DRUG REACTION CAUSED BY A MEDICATION ERROR OR OTHER CAUSATIVE EVENT?

☐ **Yes - please fill in section 2 and 3.** ☒ **No - please fill in Section 3 Reporter Details**

PLEASE NOTE THAT FOR ALL REPORTS SECTION 3 MUST BE FILLED IN

FormP010/3version02

Section 2: Medication Error Reporting

In this case not applicable

SECTION 2: MEDICATION ERROR REPORTING

IMPORTANT: 'The submission of a report does not constitute an admission that the patient, medical personnel, user facility, importer, distributor, manufacturer or the medicine itself caused or contributed to the event'.

2.1 MEDICINE(S) INVOLVED IN MEDICATION ERROR OR OTHER CAUSATIVE EVENT (EG OCCUPATIONAL EXPOSURE)

	Medicine 1	Medicine 2	Medicine 3
	If the same details were filled in section 1.2, you can leave this section blank		
Medicine Trade Name			
Active Ingredient (substance in a medicine that is biologically active)			
Form (eg: tablets, injection)			
Strength (eg: g, mg, ug)			
Dose frequency, duration, route (eg: 1 tablet, 3 dly, by mouth)			
Type of container (eg blister pack, loose strip or other)			

2.2 DATE OF EVENT

Date event occurred: ___/___/___ Date event was detected: ____/___/___

Section 3: Reporter Details

SECTION 3: REPORTER DETAILS

Details will be destroyed following transmission to the EU central side effect database Eudravigilance

Type/Circle - doctor/dentist/pharmacist/other healthcare professional/patient	
Name: Elisa Curtolo	
Address: Triq Il-Kbira	
Telephone/Mobile: 123456789	
E-mail address: elisa.curtolo.18@um.edu.mt	

Signature _____ **Date** 21/02/2021

The Medicines Authority thanks you for the time taken to fill in this form. The reporting of Adverse Drug Reactions is an important process whereby Regulatory Authorities can learn more about the medicine and its uses and take appropriate action in order to protect and enhance public health	☐ *SUPPLY OF ADR REPORT CARDS IS REQUIRED* ☐ *INFORMATION ABOUT OTHER ADRs IS REQUIRED*

PLEASE NOTE THAT FOR ALL REPORTS SECTION 3 MUST BE FILLED IN FormP010/3version02

SECTION 3 MUST BE FILLED IN FOR ALL REPORTS

Example 2

A 35-year-old female patient was administered COVID-19 VACCINE ASTRAZENECA (CHADOX1 NCOV-19) 0.5mL (batch no ABV5300) on 27/02/2021. She was hospitalised for pulmonary embolism.

The patient was not taking any concomitant medications and she was not allergic.

Decision tree

ALL PATIENT INFORMATION WILL REMAIN CONFIDENTIAL, REPORTER INFORMATION WILL BE DESTROYED

Before you start reporting please check which sections should be filled in

Please complete as much information as possible

Tick boxes where appropriate

Are you reporting an adverse drug reaction?	☒	(fill in sections 1 and 3)
Are you reporting an adverse drug reaction due to a medication error or other causative event (eg occupational exposure, abuse, overdose)?	☐	(fill in sections 1, 2 and 3)
Are you reporting a medication error or other causative event that did not lead to an adverse drug reaction?	☐	(fill in sections 2 and 3)

For a detailed explanation on how to fill in particular sections, please refer to the instructions at the back of the form

Section 1: Reporting ADRs

SECTION 1: REPORTING ADVERSE DRUG REACTIONS

1.1 PATIENT DETAILS

INITIALS _____ ☐ MALE ☒ FEMALE AGE (at time of reaction) 35 WEIGHT (in kg, if known) _____ RACE _____ AREA _____

1.2 SUSPECTED MEDICINE(S) / VACCINE(S) / BLOOD PRODUCT(S) / CANNABIS FOR MEDICINAL AND RESEARCH PURPOSES
(list the medicine you think caused the side effect)

Trade name, Active ingredient, Strength, Form, Batch no.	Dosage, frequency, route	Prescribed for	Date started dd	Date started mm	Date started yr	Date stopped dd	Date stopped mm	Date stopped yr
Medicine 1 COVID-19 VACCINE ASTRAZENECA (CHADOX1 NCOV-19) (batch no ABV5300)	0.5mL IM	COVID-19 immunisation	27	02	2021			
Medicine 2								
Medicine 3								

1.3 SUSPECTED ADVERSE DRUG REACTION (Describe each side-effect in as much detail as possible)

	Date started dd	Date started mm	Date started yr	Date stopped dd	Date stopped mm	Date stopped yr
ADR 1 Pulmonary embolism	27	02	2021			
ADR 2						
ADR 3						

Section 1: Reporting ADRs

1.4 LIST OTHER MEDICINES BEING TAKEN BY THE PATIENT (including over the counter & herbal medicinal products)

Trade name, Active Ingredient	Dosage (amount), frequency (eg: twice a day), route (eg: oral)	Prescribed for	Date started dd	Date started mm	Date started yr	Date stopped dd	Date stopped mm	Date stopped yr
NONE								

Tick boxes where appropriate

1.5 How serious do you consider this Adverse Drug Reaction?

	ADR 1	ADR 2	ADR 3
Fatal	☐	☐	☐
Life threatening	☐	☐	☐
Caused or prolonged hospitalisation	☒	☐	☐
Birth defect	☐	☐	☐
Caused disability	☐	☐	☐
Other medically significant condition	☐	☐	☐
Not Serious	☐	☐	☐

1.6 Outcome from Adverse Drug Reaction:

	ADR 1	ADR 2	ADR 3
Recovered	☐	☐	☐
Recovering	☐	☐	☐
Symptoms continuing	☐	☐	☐
Long-term effects	☐	☐	☐
Death	☐	☐	☐
Not known	☒	☐	☐

1.7 For this Adverse Drug Reaction(s):

	YES	NO
Suspect medicine 1 was stopped	☐	☐
Suspect medicine 2 was stopped	☐	☐
Suspect medicine 3 was stopped	☐	☐
Was medicine restarted	☐	☐
Manufacturer notified of this ADR	☐	☐
Treatment required for this ADR	☒	☐
If yes, which Is this the first time you reported the ADR	☐	☒

Section 1: Reporting ADRs

1.8 ADDITIONAL RELEVANT INFORMATION (if known)
(known allergies, test results, medical history, discharge summaries – information may be attached)

☐ Liver disease ☐ Kidney disease	Allergy (please describe): NONE	Pregnancy weeks
Other illnesses (please describe):		

1.9 WAS THIS ADVERSE DRUG REACTION CAUSED BY A MEDICATION ERROR OR OTHER CAUSATIVE EVENT?
☐ **Yes - please fill in section 2 and 3.** ☒ **No - please fill in Section 3 Reporter Details**

PLEASE NOTE THAT FOR ALL REPORTS SECTION 3 MUST BE FILLED IN FormP010/3version02

Section 2: Medication Error Reporting

In this case not applicable

SECTION 2: MEDICATION ERROR REPORTING

IMPORTANT: 'The submission of a report does not constitute an admission that the patient, medical personnel, user facility, importer, distributor, manufacturer or the medicine itself caused or contributed to the event'.

2.1 MEDICINE(S) INVOLVED IN MEDICATION ERROR OR OTHER CAUSATIVE EVENT (EG OCCUPATIONAL EXPOSURE)

	Medicine 1	Medicine 2	Medicine 3
If the same details were filled in section 1.2, you can leave this section blank			
Medicine Trade Name			
Active Ingredient (substance in a medicine that is biologically active)			
Form (eg: tablets, injection)			
Strength (eg: g, mg, ug)			
Dose frequency, duration, route (eg: 1 tablet, 3 dly, by mouth)			
Type of container (eg blister pack, loose strip or other)			

2.2 DATE OF EVENT
Date event occurred: ___/___/___ Date event was detected: ___/___/___

Section 3: Reporter Details

SECTION 3: REPORTER DETAILS
Details will be destroyed following transmission to the EU central side effect database Eudravigilance

Type/Circle - doctor/dentist/pharmacist/other healthcare professional/patient	
Name:	Elisa Curtolo
Address:	Triq Il-Kbira
Telephone/Mobile:	123456789
E-mail address:	elisa.curtolo.18@um.edu.mt

Signature _____ Date 27/02/2021

The Medicines Authority thanks you for the time taken to fill in this form. The reporting of Adverse Drug Reactions is an important process whereby Regulatory Authorities can learn more about the medicine and its uses and take appropriate action in order to protect and enhance public health	☐ *SUPPLY OF ADR REPORT CARDS IS REQUIRED* ☐ *INFORMATION ABOUT OTHER ADRs IS REQUIRED*

PLEASE NOTE THAT FOR ALL REPORTS SECTION 3 MUST BE FILLED IN FormP010/3version02

SECTION 3 MUST BE FILLED IN FOR ALL REPORTS

Example 3

A 80-year-old male patient was administered COVID-19 MRNA VACCINE MODERNA (CX-024414) 0.5mL (batch no XXXXXX) on 15/02/2021. After administration, the patient felt malaise, rigor and had burning of the chest. The patient was hospitalised.

Patient recovered 2 days after from malaise and chest burning and 4 days after from rigors.

Patient's concomitant medication was: VOTRIENT - PAZOPANIB HYDROCHLORIDE for renal cell carcinoma with metastasis to lungs.

Decision tree

ALL PATIENT INFORMATION WILL REMAIN CONFIDENTIAL, REPORTER INFORMATION WILL BE DESTROYED

Before you start reporting please check which sections should be filled in

Please complete as much information as possible

Tick boxes where appropriate

Are you reporting an adverse drug reaction?	[X]	(fill in sections 1 and 3)
Are you reporting an adverse drug reaction due to a medication error or other causative event (eg occupational exposure, abuse, overdose)?	☐	(fill in sections 1, 2 and 3)
Are you reporting a medication error or other causative event that did not lead to an adverse drug reaction?	☐	(fill in sections 2 and 3)

For a detailed explanation on how to fill in particular sections, please refer to the instructions at the back of the form

Section 1: Reporting ADRs

SECTION 1: REPORTING ADVERSE DRUG REACTIONS

1.1 PATIENT DETAILS

INITIALS _____ [X] MALE ☐FEMALE AGE (at time of reaction) 80 WEIGHT (in kg, if known) _____ RACE _____ AREA _____

1.2 SUSPECTED MEDICINE(S) / VACCINE(S) / BLOOD PRODUCT(S) / CANNABIS FOR MEDICINAL AND RESEARCH PURPOSES

(list the medicine you think caused the side effect)

Trade name, Active ingredient, Strength, Form, Batch no.	Dosage, frequency, route	Prescribed for	Date started (dd mm yr)	Date stopped (dd mm yr)
Medicine 1: COVID-19 MRNA VACCINE MODERNA (CX-024414) (batch no XXXXXX)	0.5mL IM	COVID-19 immunisation	15/02/2021	
Medicine 2				
Medicine 3				

1.3 SUSPECTED ADVERSE DRUG REACTION (Describe each side-effect in as much detail as possible)

	Date started (dd mm yr)	Date stopped (dd mm yr)
ADR 1: and malaise	15/02/2021	17/02/2021
ADR 2: Rigor	15/02/2021	19/02/2021
ADR 3: Chest burning	15/02/2021	17/02/2021

Section 1: Reporting ADRs

1.4 LIST OTHER MEDICINES BEING TAKEN BY THE PATIENT (including over the counter & herbal medicinal products)

Trade name, Active Ingredient	Dosage (amount), frequency (eg: twice a day), route (eg: oral)	Prescribed for	Date started dd	Date started mm	Date started yr	Date stopped dd	Date stopped mm	Date stopped yr
VOTRIENT - PAZOPANIB HYDROCHLORIDE		Renal cell carcinoma and metastasis to lungs						

Tick boxes where appropriate

1.5 How serious do you consider this Adverse Drug Reaction?

	ADR 1	ADR 2	ADR 3
Fatal	☐	☐	☐
Life threatening	☐	☐	☐
Caused or prolonged hospitalisation	☒	☒	☒
Birth defect	☐	☐	☐
Caused disability	☐	☐	☐
Other medically significant condition	☐	☐	☐
Not Serious	☐	☐	☐

1.6 Outcome from Adverse Drug Reaction:

	ADR 1	ADR 2	ADR 3
Recovered	☒	☒	☒
Recovering	☐	☐	☐
Symptoms continuing	☐	☐	☐
Long-term effects	☐	☐	☐
Death	☐	☐	☐
Not known	☐	☐	☐

1.7 For this Adverse Drug Reaction(s):

	YES	NO
Suspect medicine 1 was stopped	☐	☐
Suspect medicine 2 was stopped	☐	☐
Suspect medicine 3 was stopped	☐	☐
Was medicine restarted	☐	☐
Manufacturer notified of this ADR	☐	☐
Treatment required for this ADR	☒	☐
If yes, which Is this the first time you reported the ADR	☐	☒

Section 1: Reporting ADRs

1.8 ADDITIONAL RELEVANT INFORMATION (if known)
(known allergies, test results, medical history, discharge summaries – information may be attached)

☐ Liver disease ☐ Kidney disease	Allergy (please describe): None	Pregnancy weeks
Other illnesses (please describe):		

1.9 WAS THIS ADVERSE DRUG REACTION CAUSED BY A MEDICATION ERROR OR OTHER CAUSATIVE EVENT?

☐ **Yes - please fill in section 2 and 3.** ☒ **No - please fill in Section 3 Reporter Details**

PLEASE NOTE THAT FOR ALL REPORTS SECTION 3 MUST BE FILLED IN

FormP010/3version02

Section 2: Medication Error Reporting

In this case not applicable

SECTION 2: MEDICATION ERROR REPORTING

IMPORTANT: 'The submission of a report does not constitute an admission that the patient, medical personnel, user facility, importer, distributor, manufacturer or the medicine itself caused or contributed to the event'.

2.1 MEDICINE(S) INVOLVED IN MEDICATION ERROR OR OTHER CAUSATIVE EVENT (EG OCCUPATIONAL EXPOSURE)

	Medicine 1	Medicine 2	Medicine 3
If the same details were filled in section 1.2, you can leave this section blank			
Medicine Trade Name			
Active Ingredient (substance in a medicine that is biologically active)			
Form (eg: tablets, injection)			
Strength (eg: g, mg, ug)			
Dose frequency, duration, route (eg: 1 tablet, 3 dly, by mouth)			
Type of container (eg blister pack, loose strip or other)			

2.2 DATE OF EVENT

Date event occurred: ___/___/___ Date event was detected: ____/___/___

Section 3: Reporter Details

SECTION 3: REPORTER DETAILS

Details will be destroyed following transmission to the EU central side effect database Eudravigilance

Type/Circle - doctor/dentist/pharmacist/other healthcare professional/patient

Name: Elisa Curtolo

Address: Triq Il-Kbira

Telephone/Mobile: 123456789

E-mail address: elisa.curtolo.18@um.edu.mt

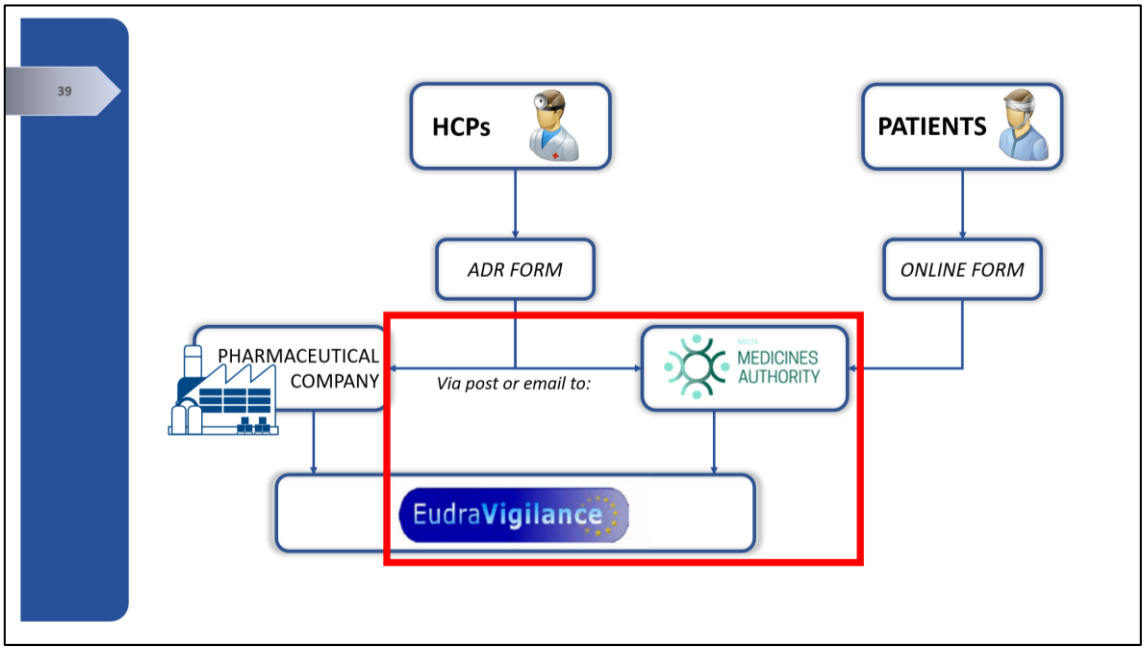
Signature _____ **Date** 19/02/2021

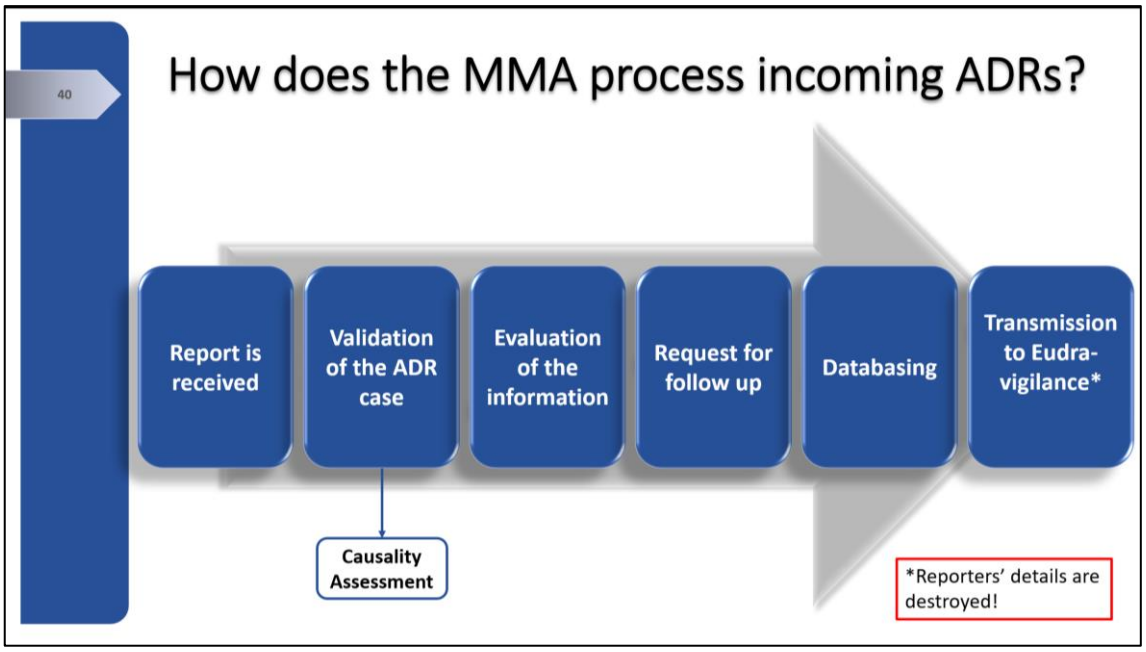
The Medicines Authority thanks you for the time taken to fill in this form. The reporting of Adverse Drug Reactions is an important process whereby Regulatory Authorities can learn more about the medicine and its uses and take appropriate action in order to protect and enhance public health	☐ *SUPPLY OF ADR REPORT CARDS IS REQUIRED* ☐ *INFORMATION ABOUT OTHER ADRs IS REQUIRED*

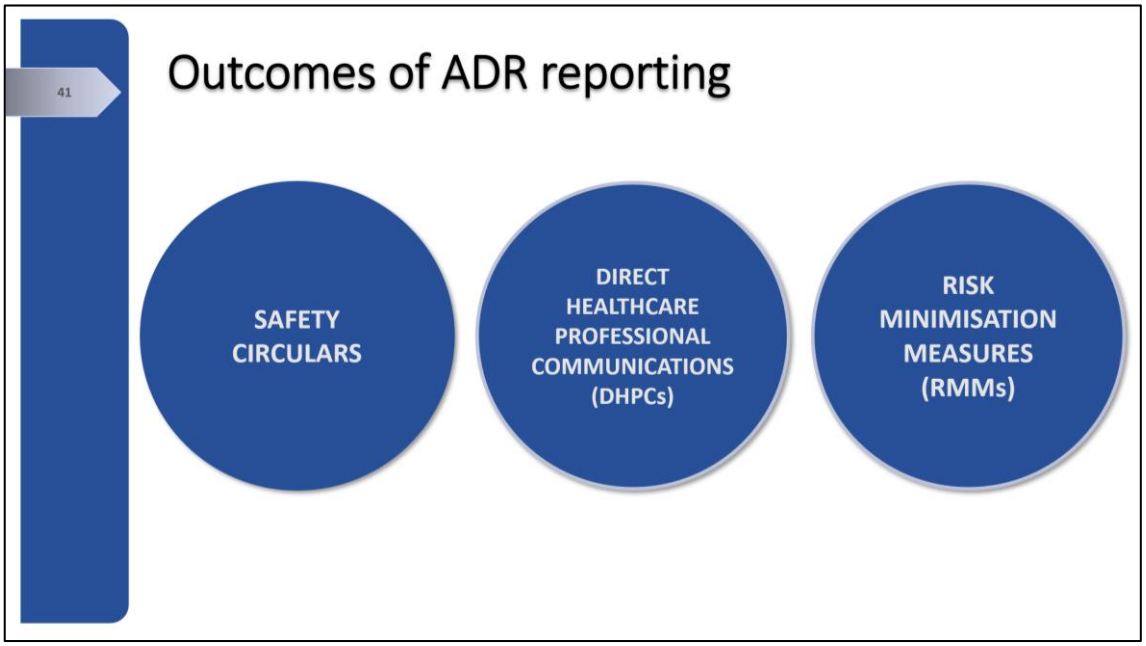
PLEASE NOTE THAT FOR ALL REPORTS SECTION 3 MUST BE FILLED IN FormP010/3version02

SECTION 3 MUST BE FILLED IN FOR ALL REPORTS

Outcomes of ADR reports




40
How does the MMA process incoming ADRs?
Report is received
Validation of the ADR case
Evaluation of the information
Request for follow up
Databasing
Transmission to Eudra-vigilance*
Causality Assessment
*Reporters' details are destroyed!


41
Outcomes of ADR reporting
SAFETY CIRCULARS
DIRECT HEALTHCARE PROFESSIONAL COMMUNICATIONS (DHPCs)
RISK MINIMISATION MEASURES (RMMs)

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Safety Circulars

Circulars issued
- by the **MMA**
- for **HCPs** and **patients**

Issued when a *safety concern* relating to the safe and effective use of a medicinal product on the market is present

Examples:
- ❑ withdrawal or suspension from the market for safety reasons
- ❑ restriction of use, new contraindications or warnings
- ❑ product defects leading to safety concerns
- ❑ Endorsement of repurposed medications

Published and archived on MMA website:
http://www.medicinesauthority.gov.mt/safetycirculars

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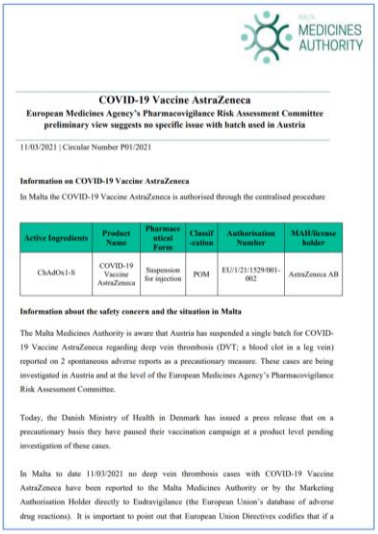
Safety Circulars - Example



MEDICINES AUTHORITY

COVID-19 Vaccine AstraZeneca

European Medicines Agency's Pharmacovigilance Risk Assessment Committee preliminary view suggests no specific issue with batch used in Austria

11/03/2021 | Circular Number P01/2021

Information on COVID-19 Vaccine AstraZeneca

In Malta the COVID-19 Vaccine AstraZeneca is authorised through the centralised procedure

Active Ingredients	Product Name	Pharmaceutical Form	Classification	Authorisation Number	MAH/license holder
ChAdOx1-S	COVID-19 Vaccine AstraZeneca	Suspension for injection	POM	EU/1/21/1529/001-002	AstraZeneca AB

Information about the safety concern and the situation in Malta

The Malta Medicines Authority is aware that Austria has suspended a single batch for COVID-19 Vaccine AstraZeneca regarding deep vein thrombosis (DVT; a blood clot in a leg vein) reported on 2 spontaneous adverse reports as a precautionary measure. These cases are being investigated in Austria and at the level of the European Medicines Agency's Pharmacovigilance Risk Assessment Committee.

Today, the Danish Ministry of Health in Denmark has issued a press release that on a precautionary basis they have paused their vaccination campaign at a product level pending investigation of these cases.

In Malta to date 11/03/2021 no deep vein thrombosis cases with COVID-19 Vaccine AstraZeneca have been reported to the Malta Medicines Authority or by the Marketing Authorisation Holder directly to Eudravigilance (the European Union's database of adverse drug reactions). It is important to point out that European Union Directives codifies that if a

- COVID-19 Vaccine AstraZeneca: PRAC investigating cases of thromboembolic events - vaccine's benefits currently still outweigh risks

Safety Circulars - Example

COVID-19 Vaccine AstraZeneca

European Medicines Agency's Pharmacovigilance Risk Assessment Committee preliminary view suggests no specific issue with batch used in Austria

11/03/2021 | Circular Number P01/2021

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Safety Circulars - Example

Information about the safety concern and the situation in Malta

The Malta Medicines Authority is aware that Austria has suspended a single batch for COVID-19 Vaccine AstraZeneca regarding deep vein thrombosis (DVT; a blood clot in a leg vein) reported on 2 spontaneous adverse reports as a precautionary measure. These cases are being investigated in Austria and at the level of the European Medicines Agency's Pharmacovigilance Risk Assessment Committee.

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Safety Circulars - Example

national suspension of a medicinal product occurs in any member state at the level of the marketing authorisation an article 107i procedure has to be triggered at the level of the European Union and the European Medicines Agency. To date, this required procedure has not been triggered by Denmark or Austria, and therefore the benefit/risk of the COVID-19 Vaccine AstraZeneca remains positive in the authorised indications.

As per the European Medicines Agency's press release of 10/3/2020:

There is currently no indication that vaccination has caused these conditions, which are not listed as side effects with this vaccine.

Batch ABV5300 was delivered to 17 European Union countries[1] and comprises 1 million doses of the vaccine. Some EU countries[2] have also subsequently suspended this batch as a precautionary measure, while a full investigation is ongoing. Although a quality defect is considered unlikely at this stage, the batch quality is being investigated.

Safety Circulars - Example

European Medicines Agency's safety committee Pharmacovigilance Risk Assessment Committee is reviewing this issue; it is investigating the cases reported with the batch as well as all other cases of thromboembolic events, and other conditions related to blood clots, reported post-vaccination. The information available so far indicates that the number of thromboembolic events in vaccinated people is no higher than that seen in the general population. As of 9 March 2021, 22 cases of thromboembolic events had been reported among the 3 million people vaccinated with COVID-19 Vaccine AstraZeneca in the European Economic Area.

The Pharmacovigilance Risk Assessment Committee will continue its assessment of any potential issue with the batch as well as its review of thromboembolic events and related conditions.

The European Medicines Agency will further communicate as the assessment progresses.

For more information please see the European Medicines Agency's press release

[1] Austria, Bulgaria, Cyprus, Denmark, Estonia, France, Greece, Iceland, Ireland, Latvia, Lithuania, Luxemburg, Malta, the Netherlands, Poland, Spain, Sweden.
[2] As of 9 March 2021: Estonia, Lithuania, Luxembourg, Latvia

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Direct Healthcare Professional Communications (DHPCs)

Letters sent by post or email
- by the **MAH**
- to **HCPs**

Informing them of "the need to take certain *actions* or *adapt their practices* in relation to a medicinal product"[1]

Examples:
- ❑ Suspension or withdrawal of a marketing authorisation for safety reasons
- ❑ An important change, e.g.: a restriction of indication, a new contraindication, or a change in the recommended dose
- ❑ Restriction in availability or discontinuation of a medicine
- ❑ Quality problems with a medicine

Archived on MMA website:
http://www.medicinesauthority.gov.mt/dhpc

[1] European Medicines Agency [Internet]. Amsterdam; c1995-2020 [cited 2020 Nov 20]. Guideline on good pharmacovigilance practices (GVP) Module XV – Safety communication (Rev 1). Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xv-safety-communication-rev-1_en.pdf

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DHPCs - example

CENTRAL PROCUREMENT & SUPPLIES UNIT
MINISTRY FOR HEALTH
UB002 San Gwann Industrial Estate, San Gwann. SGN3000
Tel: (+356) 2540 4000 E-mail: info.cpsu@gov.mt

24 September 2020

Direct Healthcare Professional Communication

Caution in Use: Amoxicillin Sodium 250mg Powder for Solution for Injection
CPSU Product licence AA565/26703 (Wockhardt; PL29831/0010)

Following a Class 4 Drug Alert in the UK regarding Wockhardt UK's Amoxicillin, the Central procurement and Supplies Unit in agreement with the Malta Medicines Authority would like to inform you of the following:

Summary

- **Amoxicillin Sodium 250mg Powder for Solution for Injection (all strengths and all batches) is associated with reports of extravasation and injections site reactions in neonates and infants (below 1 year old)**
- **Although no root cause has been confirmed for these events, an investigation identified contributing factors, which are currently considered to be resolved**
- **Based on MHRA's review of available data, the Commission on Human Medicines' Paediatric Medicine Expert Advisory Group (PMEAG) has advised that Wockhardt UK's Amoxicillin Sodium Powder for Solution for Injection can be used with caution in neonates and infants**
- **Healthcare professionals are asked to exercise caution when using these products and monitor the cannula site before, during and after administration; administration should be stopped immediately if extravasation or injection site reactions are suspected**
- **Healthcare professionals should report extravasation events and any suspected adverse drug reactions with these products directly to the Malta Medicines Authority via the adverse drug reaction form.**

Background

In July 2014, a Class 4 Drug Alert was issued in the UK asking healthcare professionals not to use Wockhardt UK Amoxicillin Powder for Solution for Injection (all strengths and all batches) in neonates and infants (below 1 year old), following receipt of a number of reports of extravasation and injections site reactions.

- **Caution in Use**: Amoxicillin Sodium 250mg Powder for Solution for Injection
- Following a Class 4 Drug Alert in the UK regarding Wockhardt UK's Amoxicillin

DHPC - Example

24 September 2020

Direct Healthcare Professional Communication

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DHPC - Example

Background

In July 2014, a Class 4 Drug Alert was issued in the UK asking healthcare professionals not to use Wockhardt UK Amoxicillin Powder for Solution for Injection (all strengths and all batches) in neonates and infants (below 1 year old), following receipt of a number of reports of extravasation and injections site reactions.

This was followed by a Class 2 Drug Alert, recalling three batches of Wockhardt UK's Amoxicillin Sodium 500mg Powder for Solution for Injection, which were investigated. Although the recalled batches had parameters out-of-trend with usual batches, they were not identified as defective.

Wockhardt UK has revised the finished product and Active Pharmaceutical Ingredient specifications to include a tightened pH specification and introduced limits for osmolality for the reconstituted product.

In May 2020, following a MHRA review of all data available since the alert, the Committee on Human Medicines' PMEAG advised that Wockhardt UK's Amoxicillin Sodium Powder for Solution for Injection could be used in neonates and infants (below 1 year old).

DHPC - Example

Advice for Healthcare Professionals:
Caution and monitoring should be exercised during the use of these products for the development of extravasation or injection site reactions.

In order to minimise the risk of extravasation or injection site reactions a number of precautions should be taken:

- Wockhardt UK's Amoxicillin Sodium Powder for Solution for Injection should be prepared and administered in accordance with section 4.2, Method of administration, of the Summary of Product Characteristics.
- For more information, see https://www.medicines.org.uk/emc/product/1358/smpc
- The cannula site should be observed and monitored before, during and after administration of Amoxicillin Sodium Powder for Solution for Injection.
- Patency of the cannula should be maintained.
- If extravasation or injection site reactions are suspected, the administration of Amoxicillin Sodium Powder for Solution for Injection should be stopped immediately and the appropriate procedures in line with local guidelines should be followed.

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Risk Minimisation Measures (RMMs)

Educational material
- by the **MMA**
- for **HCPs** and **patients**

To understand the *risk* associated with a medicinal product and the ways in which the *risk can be minimised*

*"the **right medicine**, at the **right dose**, at the **right time**, to the **right patient** and with the **right information** and **monitoring**"*[2]

Examples:
- Leaflets
- Brochures
- Training
- Restrictions in prescribing and dispensing

Archived on MMA website:
http://medicinesauthority.gov.mt/rmm

[2]European Medicines Agency [Internet]. Amsterdam; c1995-2020 [cited 2020 Nov 20]. Guideline on good pharmacovigilance practices (GVP) Module XVI – Risk minimisation measures: selection of tools and effectiveness indicators (Rev 2). Available from: https://www.ema.europa.eu/en/documents/scientific-guideline/guideline-good-pharmacovigilance-practices-module-xv-safety-communication-rev-1_en.pdf

RMMs – Example - HCPS

RMMs – Example - patients

Patient alert card

Rivarolto® 2.5 mg film-coated tablets ☐
Rivarolto® 10 mg film-coated tablets ☐
Rivarolto® 15 mg film-coated tablets ☐
Rivarolto® 20 mg film-coated tablets ☐

KRKA

- **Keep this card with you at all times**
- **Present this card to every physician or dentist prior to treatment**

Information for health care providers:
- INR values should not be used as they are not a dependable measure of the anticoagulant activity of Rivarolto®.

What should I know about Rivarolto®?
- Rivarolto® thins the blood, which prevents you from getting dangerous blood clots.
- Rivarolto® must be taken exactly as prescribed by your doctor. To ensure optimal protection from blood clots, **never skip a dose**.
- You must not stop taking Rivarolto® without first talking to your doctor as your risk of blood clots may increase.
- Tell your health care provider about any other medicines you are currently taking, took recently or intend to start taking, before you start Rivarolto®.
- Tell your health care provider that you are taking Rivarolto® before any surgery or invasive procedure.

When should I seek advice from my health care provider?
When taking a blood thinner such as Rivarolto® it is important to be aware of its possible side effects. Bleeding is the most common side effect. Do not start taking Rivarolto® if you know you are at risk of bleeding, without first discussing this with your doctor. Tell your health care provider straight away if you have any signs or symptoms of bleeding such as the following:
- pain
- swelling or discomfort
- headache, dizziness or weakness
- unusual bruising, nosebleeds, bleeding of gums, cuts that take a long time to stop bleeding
- menstrual flow or vaginal bleeding that is heavier than normal
- blood in your urine which may be pink or brown, red or black stools
- coughing up blood, or vomiting blood or material that looks like coffee grounds

How do I take Rivarolto®?
- To ensure optimal protection, Rivarolto®
  - 2.5 mg can be taken with or without food
  - 10 mg can be taken with or without food
  - 15 mg must be taken with food
  - 20 mg must be taken with food

Recognising ADRs in practice

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Recognising an ADR - Key points

- Patient is taking right medication at right dose
- Onset of suspected ADR after taking the drug
- Time beginning drug treatment – Time onset of the event
- Discontinue drug or ↓ dose. If appropriate, restart drug treatment
- Alternative causes
- Up-to-date literature and personal experience
- Report any suspected ADR

Couper M. Safety of medicines - a guide to detecting and reporting adverse drug reaction - Why health professionals need to take action [Internet]. WHO; 2002 [Cited 2021 Mar 15]. Available from: http://www.digicollection.org/hss/en/d/Jh2992e/10.html

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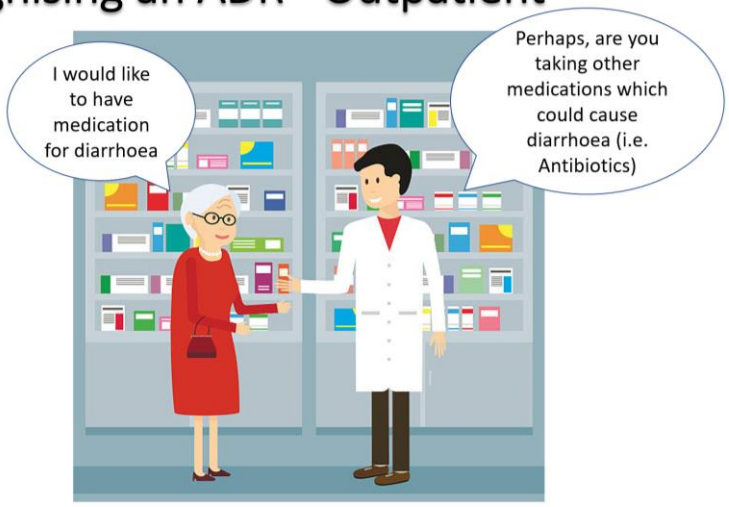
Recognising an ADR - Outpatient



Schatz SN, Weber RJ. Adverse drug reactions, Pharmacotherapy Self-Assessment Program (PSAP). 2015; 1(1):5-21

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Recognising an ADR - Inpatient

Schatz SN, Weber RJ. Adverse drug reactions, Pharmacotherapy Self-Assessment Program (PSAP). 2015; 1(1):5-21

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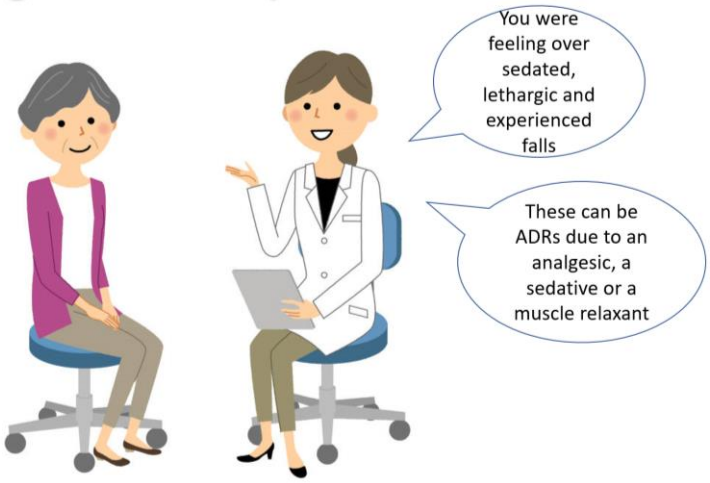
Recognising an ADR - Inpatient

Schatz SN, Weber RJ. Adverse drug reactions, Pharmacotherapy Self-Assessment Program (PSAP). 2015; 1(1):5-21

61

Recognising an ADR - Inpatient



Schatz SN, Weber RJ. Adverse drug reactions, Pharmacotherapy Self-Assessment Program (PSAP). 2015; 1(1):5-21

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Safety Representative

- ADR reporting and updates on pharmacovigilance activities
- Pharmacist working closely to both the HCPs and MMA

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Safety Representative

ROLES

- Safe and rational use of medicinal products
- ADR reporting
- Questions related to safety
- Medication errors
- Bridge between National Competent Authority and HCPs

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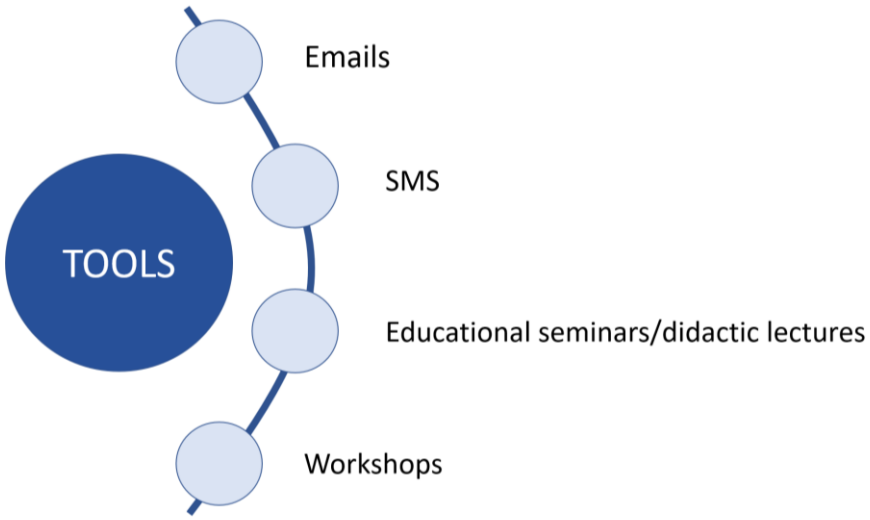
Safety Representative



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Useful links

- Malta Medicines Authority: http://www.medicinesauthority.gov.mt/
- ADR reporting form for **HCPs:** http://www.medicinesauthority.gov.mt/file.aspx?f=4496
- ADR reporting form for **patients:** http://www.medicinesauthority.gov.mt/form-details?surID=35&cat=3

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Useful links

- Safety information:

  http://www.medicinesauthority.gov.mt/safetyinfo?l=1

  - Safety circulars: http://www.medicinesauthority.gov.mt/safetycirculars
  - DHPCs: http://www.medicinesauthority.gov.mt/dhpc
  - RMMs: http://www.medicinesauthority.gov.mt/rmm

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Open Discussion (cases)

- 07-Mar: Austria suspended a batch (ABV5300) of covid-19 Vaccine AstraZeneca after a 49-year-old woman died from multiple thrombosis 10 days after taking the vaccine and a second one (35-year-old) hospitalised for pulmonary embolism after vaccine administration
- 09-Mar: Estonia, Latvia, Lithuania and Luxembourg suspended the same batch
- 11-Mar: Denmark was the first country to suspend covid-19 vaccine AstraZeneca. Norway (3 hours after), Iceland, Bulgaria, Ireland (yesterday) followed
- 11-Mar: Italy suspended the batch ABV2856
- 12-Mar: Romania suspended the batch ABV2856
- **15-Mar: Germany, Netherlands, Italy, France and Spain: temporal suspension**
- UK is still rolling out covid-19 Vaccine AstraZeneca

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Open Discussion (outcomes)

- **AstraZeneca:** 15 DVT events and 22 pulmonary embolism among those given the vaccine → n° of thromboembolic events in vaccinated people not higher than the one observed in the general population
- **European Medicines Agency (EMA)** is investigating reports of blood clots in vaccinated people but presently there is no firm evidence of a link between the vaccine and blood clot incidents
  - 10/03/21: 30 cases of thromboembolic events among 5 million vaccinated with Covid-19 AstraZeneca vaccine in the EEA
- **Pharmacovigilance Risk Assessment Committee (PRAC):** benefits are higher than risks. People can still get vaccine while investigations are ongoing
- **WHO:** there is no reason to stop administration of AstraZeneca vaccination

L-Università ta' Malta

Thank you for your participation

Evaluation form (link):
https://docs.google.com/forms/d/e/1FAIpQLSdX9sRFuxWyygOgrtslym_P2nItkaBBH28MoeStqkdRdgsOhw/viewform?usp=sf_link

Elisa Curtolo

elisa.curtolo.18@um.edu.mt

Appendix 6: Evaluation forms of educational webinars

An innovative approach to Pharmacovigilance

Elisa Curtolo

PharmD student

Department of Pharmacy, University of Malta

Introduction and Instructions

Dear Participant,

An educational webinar titled "Pharmacovigilance in the time of a pandemic crisis – Adverse Drug Reaction reporting" is being conducted as part of my Doctorate in Pharmacy research at the Department of Pharmacy, University of Malta, under the supervision of Professor Anthony Serracino-Inglott and Dr Janis Vella Szijj.

Kindly complete the evaluation form after following the educational webinar.

All healthcare professionals are eligible to participate.

Responses will only be accessed by research team members.

Should you have any queries, kindly contact the researcher Elisa Curtolo:

Email: elisa.curtolo.18@um.edu.mt

Thank you very much for your participation

SECTION 1: DEMOGRAPHICS

1. **Gender** ☐ Male ☐ Female ☐ Other

2. **Age (years)** _____

3. **Profession**

   ☐ Pharmacist ☐ Medical Doctor ☐ Dentist ☐ Nurse

4. **Area of practice**

   ☐ Community ☐ Academia

   ☐ Hospital ☐ Industry

   ☐ Regulatory ☐ Nursing Home

   ☐ Health Centre

   ☐ Other _____

5. **Years of practice** _____

SECTION 2: EVALUATION OF EDUCATIONAL SEMINAR

N°	Statement	1 (Strongly disagree)	2 (Disagree)	3 (Neutral)	4 (Agree)	5 (Strongly agree)
Educational content						
6.	The sequence of material was appropriate					
7.	Information in the educational seminar was clearly presented					
8.	Information in the educational seminar was comprehensive					
Relevance to practice						
9.	The educational seminar was relevant for my practice					
10.	The educational seminar made me more aware of the importance of ADR reporting					
11.	The educational seminar helped me overcome barriers toward ADR reporting					
In conclusion						
12.	Following the educational seminar, I am confident with ADR reporting					
13.	The educational seminar met my expectations					

14. Any additional feedback or suggestions related to the educational seminar may be included below

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Thank you

An innovative approach to Pharmacovigilance

Elisa Curtolo

PharmD student

Department of Pharmacy, University of Malta

Introduction and Instructions

Dear Participant,

An educational webinar titled "Pharmacovigilance in the time of a pandemic crisis – Adverse Drug Reaction reporting - Part 2 Outcomes" is being conducted as part of my Doctorate in Pharmacy research at the Department of Pharmacy, University of Malta, under the supervision of Professor Anthony Serracino-Inglott and Dr Janis Vella Szijj.

Kindly complete the evaluation form after following the educational webinar.

All healthcare professionals are eligible to participate.

Responses will only be accessed by research team members.

Should you have any queries, kindly contact the researcher Elisa Curtolo:

Email: elisa.curtolo.18@um.edu.mt

Thank you very much for your participation

SECTION 1: DEMOGRAPHICS

1. **Gender** ☐ Male ☐ Female ☐ Other

2. **Age (years)** _____

3. **Profession**

   ☐ Pharmacist ☐ Medical Doctor ☐ Dentist ☐ Nurse

4. **Area of practice**

   ☐ Community ☐ Academia

   ☐ Hospital ☐ Industry

   ☐ Regulatory ☐ Nursing Home

   ☐ Health Centre

   ☐ Other _____

5. **Years of practice** _____

SECTION 2: EVALUATION OF EDUCATIONAL SEMINAR

N°	Statement	1 (Strongly disagree)	2 (Disagree)	3 (Neutral)	4 (Agree)	5 (Strongly agree)
Educational content						
6.	The sequence of material was appropriate					
7.	Information in the educational seminar was clearly presented					
8.	Information in the educational seminar was comprehensive					
Relevance to practice						
9.	The educational seminar was relevant for my practice					
10.	The educational seminar made me more aware of the importance of ADR reporting					
11.	The educational seminar helped me overcome barriers toward ADR reporting					
In conclusion						
12.	Following the educational seminar, I am confident with ADR reporting					
13.	The educational seminar met my expectations					
14.	I agree with the idea of the Safety Representative (SR)					

15. Any additional feedback or suggestions related to the educational seminar may be included below

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Thank you