Drug Intelligence and Access to Medicine

A thesis submitted in partial fulfilment

of the requirements of the Degree

of Doctorate in Pharmacy

CAROLINE MUSCAT

Department of Pharmacy

University of Malta

2020

To my dearest family and friends whose unyielding love, support and encouragement have inspired me to pursue and complete this research.

Acknowledgements

I would like to thank my thesis supervisor, Professor Anthony Serracino-Inglott, for suggesting this original title and for his constructive criticism throughout. Thank you, Professor, for recognising my ability to undertake this Doctorate degree.

I would like to express my sincere gratitude to the Head of the Department of Pharmacy at the University of Malta, Professor Lilian M. Azzopardi and to all those who have contributed to my educational development in some way or another. You have all been part of this challenging journey and your guidance has been crucial to its successful completion.

I would like to thank my colleagues at the Malta Medicines Authority, especially the Director of Scientific and Regulatory Operations, Dr Annalise Attard and the Director for Advanced Scientific Initiatives, Dr Luana Mifsud Buhagiar for their precious friendship and continuous encouragement.

Heartfelt thanks go to all of my true friends with whom I have shared both the good times and the tough periods in my life.

Finally, I am deeply grateful to my family for their constant love and unwavering support. I am truly blessed to be surrounded by such lovely people.

Abstract

Access to safe, effective and good quality medicines is an evolving, complex and multifactorial challenge which has significant impact on public health and may contribute to health inequalities. This research aimed to develop a rational and prompt medicines accessibility framework. The objectives related to enhancing access to medicines were to: 1 Analyse retrospective queries and 2 Propose a framework to deal with access issues.

The methodology involved two stages: 1 Analysing retrospectively access queries recorded at the Medicines Intelligence and Access Unit within the Malta Medicines Authority. A focus group was set up to identify patient-related barriers to access medicines and to develop a risk-based approach to assess lack of access alongside patient medicines needs. 2 Devising an innovative framework to enhance access to medicines by acquiring medicines intelligence and analysing real case scenarios.

Observations and corresponding results progressed across the two stages: 1 All the 480 retrospective queries recorded at the Medicines Intelligence and Access Unit over a 60-month period (June 2014 and June 2019) were analysed. The focus group classified the access queries into four categories which were identified as barriers to access medicines: (i) safety (n=201, 42%) (ii) availability (n=143, 30%), (iii) pharmacoeconomic (n=97, 23%) and (iv) shortages (n=39, 8%). A risk-based approach was adopted to assess the outcomes of the access issues on patient medicines needs. The focus group recommended to classify risk by drawing on the classification of findings of the Good Manufacturing Practice quality management system and categorise risk as critical, major and other. 2 A scientific framework based on risk identification, access implications and medicines intelligence was devised to address access issues. Medicines intelligence on access issues was acquired through participation in fora and

communication with the patient. Two hundred and nineteen critical risk access queries were evaluated through case scenarios in line with the category of barriers to access which was identified. Critical risk related to safety was due to adverse effects related to the change of the medicinal product manufacturer such as a generic or biosimilar medicine (n=12, 5.5%) and contamination of active pharmaceutical ingredients with nitrosamine impurities (n=175, 79.9%). The latter was associated with a disruptive occurrence and was identified as an outlier. Availability issues were critical when the medicine was not marketed (n=8, 4%) or not listed on the Government Formulary List (n=3, 1.4%). Pharmacoeconomic issues, classified as critical (n=4, 1.8%), were associated with the high cost of medicines. Critical risk related to shortages occurred due to disruptions in the supply chain (n=15, 6.8%) and withdrawal of the marketing authorisation (n=2, 0.9%). For each case scenario, patient-centered medicines intelligence interventions were recommended such as the proposal of a standard operating procedure for the inpatient pharmacy to prepare extemporaneous preparations of adrenaline injections instead of commercially unavailable adrenaline autoinjectors.

An innovative framework to detect, address and mitigate access issues based on medicines intelligence and risk identification was developed to proactively enhance access to medicines in a personalised care approach.

Keywords

Access - Availability - Barriers to access - Case scenarios - Medicines intelligence - Pharmacoeconomics - Risk - Safety - Shortages

Table of Contents

List of Tables

List of Figures

List of Appendices

List of Abbreviations

COVID-19	Coronavirus disease 2019
CPSU	Central Procurement and Supplies Unit
DIKW	Data, Information, Knowledge and Wisdom
EMA	European Medicines Agency
EML	Essential Medicines List
EU	European Union
FREC	Faculty Research Ethics Committee
GFL	Government Formulary List
HIV	Human Immunodeficiency Virus
HMA	Heads of Medicines Agencies
INN	International Non-proprietary Names
INR	International Normalised Ratio
MIAU	Medicines Intelligence and Access Unit
MMA	Malta Medicines Authority
POYC	Pharmacy of Your Choice Scheme
TRIPS	Trade-Related Aspects of Intellectual Property Rights
UREC	University of Malta Research and Ethics Committee
WHO	World Health Organisation

Chapter One

Introduction

1.1 Evolution of access to medicines

Medicine knows its origin in 460 BC from the birth of Hippocrates, the Greek father of medicine (Hajar, 2015). Hippocrates described scientifically typical illnesses and their treatment and prescribed a tree extract, 'salycasia' a derivative of aspirin for pain relief (Grammaticos and Diamantis, 2008). Natural products and healing methods were used to alleviate symptoms and treat diseases in traditional medicine (Yuan et al., 2016).

Modern medicine emerged after the Industrial Revolution in the 18th century through scientific discoveries and inventions as characterised by aspirin which became a global commercial success[1]. In 1921, Sir Frederick Banting and his colleagues isolated the hormone insulin. This revolutionised the treatment of diabetes which was a fatal illness (Rosenfeld, 2013). A major breakthrough was the first antibacterial, penicillin discovered in 1928 by serendipity by Sir Alexander Fleming (Fleming, 1929). In 1943, clinical trials showed that penicillin was an effective antibiotic and its production was scaled up to be available to treat wounded soldiers during World War II[2]. Modern medicine has effectively reduced mortality from common infections and extended the lives of millions of patients with chronic diseases. Since the mass manufacturing of penicillin in the 1940s, the pharmaceutical industry has continuously progressed to provide access to medicines to optimise patient health outcomes[3].

[1] Medical News Today. What is modern medicine? 2018 [cited 2020 May 18] Available from: URL: https://www.medicalnewstoday.com/articles/323538

[2] Mailer JS, Mason B. Penicillin: Medicine's wartime wonder drug and its production at Peoria, Illinois. 2001 [cited 2020 May 18] Available from: URL: https://www.lib.niu.edu/2001/iht810139.html

[3] Walsh R. A history of the pharmaceutical industry. 2010 [cited 2020 May 18] Available from: URL: https://pharmaphorum.com/articles/a_history_of_the_pharmaceutical_industry/

1.1.1 The right to health

"The enjoyment of the highest attainable standard of health is one of the fundamental rights of every human being without distinction of race, religion, political belief, economic or social condition" – World Health Organisation 1946 Constitution

World Health Organisation. Constitution of the World Health Organisation. American Journal of Public Health. 1946; 36(11):1315-1323.

The right to health promotes access to medicines in a global manner and ensures equality in distribution independent of race, age, beliefs, orientation and other factors that could distinguish between one member of society and another. The right to health was emphasised in the Constitution of the World Health Organisation (WHO), the Universal Declaration of Human Rights and the International Covenant on Economic, Social, and Cultural Rights. The Doha Declaration on Trade-Related Aspects of Intellectual Property Rights (TRIPS) and Public Health affirmed that every individual has the right to access medicines which are determined to be essential[4]. Access to medicines is a fundamental element in the continuum of healthcare provision to promote the wellbeing of all individuals[5].

[4] World Trade Organisation. Declaration on the TRIPS agreement and public health. Doha. 2001 [cited 2020 May 18] Available from: URL: https://www.wto.org/english/thewto_e/minist_e/min01_e/mindecl_trips_e.htm

[5] United Nations. The Sustainable Development Goals Report 2019. New York. 2019 [cited 2020 May 18] Available from: URL: https://doi.org/10.18356/55eb9109-en.

1.2 Essential medicines

The WHO defines 'essential medicines as medicines that address the priority healthcare needs of a specific population'[6]. In a functioning healthcare system, essential medicines are accessible in appropriate dosage forms, in adequate amounts, with assured quality and at an affordable price (Manikandan, 2015; Bigdeli et al., 2018).

1.2.l The WHO essential medicines list

The WHO Essential Medicines List (EML) was introduced in 1977 with the aim to serve as a forward-looking global guidance for the development of healthcare system formularies. Medicines included in the EML are determined by their estimated present and future public health relevance, clinical efficacy, safety and cost effectiveness.

The Essential Medicines List which is updated every two years embodies the need to frequently update the selection of medicines to reflect novel options for emerging diseases, varying therapeutic patterns and evolving healthcare needs[6]. The 2019 EML includes 460 medicines in contrast to the 212 medicines published in the 1977 EML[7]. These medicines are deemed essential for addressing the most important global public health needs.

[6] World Health Organisation. Essential medicines and health products. 2020 [cited 2020 May 18] Available from: URL: https://www.who.int/medicines/services/essmedicines_def/en/

[7] World Health Organisation. World Health Organisation Model List of Essential Medicines 21st List. Geneva. 2019 [cited 2020 May 18] Available from: URL: https://www.who.int/medicines/publications/essentialmedicines/en/

The concept of essential medicines has evolved through the years beyond the selection of off-patent medicines to include innovative medicines, sustainable supply chains, equity in access, efficiency, rational use of medicines and affordability for both patients and health systems[8]. In 2001, antiretroviral medicines indicated in human immunodeficiency virus (HIV) were included in the EML even though that the medicines were considered too expensive to be included in the EML of 1999. The listing on the EML prompted the pharmaceutical industry to reduce the price and improve access to antiretroviral medicines. Since then, innovative medicines have been included in the EML for the treatment of life-threatening conditions such as tuberculosis, hepatitis C and cancer[9]. The scope behind including high-cost medicines is to induce positive dialogue between countries and pharmaceutical stakeholders to reduce cost and enhance access to innovative medicines.

[8] Bigdeli M, Peters D, Wagner A. Medicines in health systems: Advancing access, affordability and appropriate use. Alliance for Health Policy Systems and WHO. Geneva. 2014 [cited 2020 May 18] Available from: URL: https://www.who.int/alliance-hpsr/resources/FR_webfinal_v1.pdf

[9] Lo C. WHO's Essential Medicines List: discussing innovation and access. Pharmaceutical Technology. 2019 [cited 2020 May 18] Available from: URL: https://www.pharmaceutical-technology.com/features/who-essential-medicines-list/

1.2.2 Drug formularies

Formularies are lists of approved evidence-based medicines that direct medicine prescribing in healthcare systems (Woodhouse, 1994). The purpose of a drug formulary is to provide high-quality care using the most cost-effective medications which are easily accessible through the healthcare system. The formulary has a limited number of medicines listed according to the international non-proprietary names (INN) which have been selected on criteria related to proven quality, safety, efficacy and cost (Van Rossum et al., 2016). When a medicine is not listed on a formulary, the patient will experience out-of-pocket costs in order to be able to administer the prescribed medicine. In order to reflect changing therapeutic needs, formularies should be reviewed regularly and updated by adding new medicines and deleting medicines which are no longer deemed to be cost-effective[10].

A comprehensive and active formulary provides many benefits in optimising patient care at decreased cost through improved selection, good practice guidance for prescribers and rational use of medicines[11]. The formulary system also supports financial management and expenditure on medicines by making procurement and inventory management more efficient (Jones and Cronin, 2000; Morgan et al., 2009).

[10] The Kennedy Forum. A consumer guide to drug formularies: Understanding the fundamentals of behavioural health medications. 2017 [cited 2020 May 18] Available from: URL: https://www.paritytrack.org/issue_briefs/a-consumer-guide-to-drug-formularies-understanding-the-fundamentals-of-behavioral-health-medications/

[11] Management Sciences for Health and World Health Organisation. Drug and Therapeutics Committee Training Course. 2007 [cited 2020 May 18] Available from: URL: https://www.who.int/medicines/technical_briefing/tbs/02-PG_Formulary-Management_final-08.pdf

1.3 Concepts related to access

Access is a comprehensive, dynamic and vital element in the continuum of healthcare provision. Diverse determinates of access are presented in literature that consider the demand and supply aspects of healthcare system operations as well as the processes involved for consumers to obtain care and benefit from healthcare services (Levesque et al., 2013).

1.3.1 Dimensions of access

1.3.1.1 Access dimensions according to WHO

The WHO equitable access to essential medicines framework presents four dimensions to guide pharmaceutical policy formulation and unite actions to enhance access to medicines[12]. The framework indicates four factors that are fundamental to ensure access to medicines in national health systems (Bigdeli et al., 2013):

i. **Essential medicine use** through the evolvement of drug formularies and treatment guidelines leading to more planned prescribing and enhanced patient safety;

ii. **Fair prices** of medicines for healthcare systems and patients which is pursued through price competition, bulk procurement and generic medicine policies;

[12] World Health Organisation. Equitable access to essential medicines: a framework for collective action. WHO policy perspectives on medicines. Geneva. 2004 [cited 2020 May 18] Available from: URL: https://apps.who.int/iris/bitstream/handle/10665/68571/WHO_EDM_2004.4.pdf?sequence=1

iii. **Pharmacoeconomics** which takes into consideration adequate funding levels and equitable financing systems to reduce the burden of out-of-pocket spending and exorbitant expenditures on medicines;

iv. **Availability of medicines** which must be supported through organised acquisition of medicines, reasonable application of regulatory sciences and the use of digitalised technology.

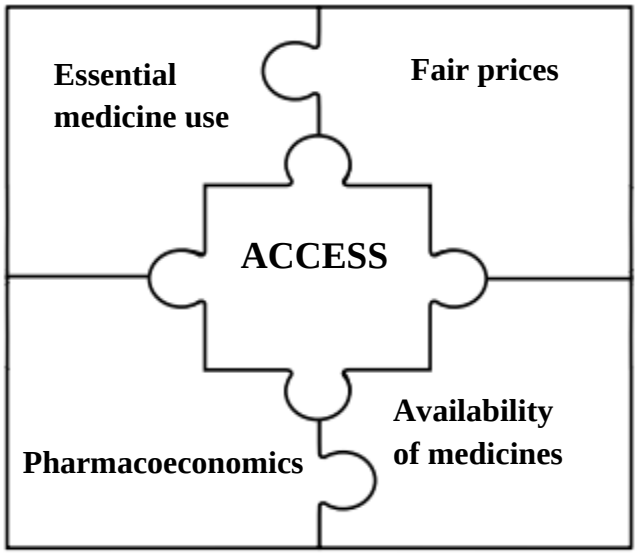

Figure 1.1: Access framework based on WHO principles

Figure based on: World Health Organisation. Equitable access to essential medicines: a framework for collective action. WHO policy perspectives on medicines. Geneva. 2004 [cited 2020 May 18] Available from: URL: https://apps.who.int /iris/bitstream/handle/10665/68571/WHO_EDM_2004.4.pdf?sequence=1

1.3.1.2 Introducing six A's of access

Penchansky and Thomas (1981) introduced a taxonomic definition of access based on determinants of use proposed by utilisation theorists. Five dimensions of access to care were identified in the theory of access of Penchansky and Thomas which described the expectations of the patient related to their needs and desires. Saurman (2016) indicated that awareness is also an integral dimension of access and should be applied when using the theory developed by Penchansky and Thomas to monitor, evaluate and improve access to healthcare.

The concept of access is complex and multidimensional. There are six dimensions of access: acceptability, accessibility, adequacy, affordability, availability and awareness (Penchansky and Thomas, 1981; Saurman, 2016). Each dimension is essential, interdependent and interrelated to the other aspects in promoting or hindering access to medicines.

i. **Acceptability**

   Acceptability considers the predisposing and enabling factors of the individual in seeking healthcare services. This dimension focuses on communication and cultural relationships between the patient and the provider of the service (Goodson, 2010). Patient health outcomes are optimised when there is concordance rather than patient compliance with the pharmaceutical care plan (Chatterjee, 2006; Cousin et al., 2012; Cushing and Metcalfe, 2007).

ii. **Accessibility**

Accessibility is determined by how services are effectively available for utilisation which is dependent on the acceptability of services, proximity and the adequacy of supply. A case example is the time it takes for patients to obtain the necessary healthcare.

iii. **Adequacy**

Adequacy reflects the relationship between the needs of the patient and the way supply resources are coordinated to meet the expectations of the patient. While medicines may be physically available, affordable, and acceptable to consumers, the adequacy dimension evaluates convenience and patient-centered aspects.

iv. **Affordability**

Affordability is a measure of the economic capacity of patients to pay for healthcare services without financial burden. Indirect costs, opportunity costs and the perception of value of the patient are also measured in the affordability dimension of access.

v. **Availability**

Availability refers to the adequate provision of healthcare professionals and healthcare facilities such as pharmacies, clinics and hospitals that are available in reasonable time and proximity in order for patients to benefit from the health services.

vi. **Awareness**

Awareness reflects the importance of effective communication and information strategies on healthcare services to curate the health needs of patients. The awareness dimension supports the empowerment of healthcare professionals and patients to understand and apply robust information to make health-related decisions.

Access is a major concern in healthcare policy. Actions to enhance access are effective if the interdependence between the different dimensions of access is recognised and effective measures of these dimensions are adopted in the basis of healthcare policy changes (McLaughlin and Wyszewianski, 2002). As described in the theory of access of Penchansky and Thomas (1981), the better the relation between the desires and needs of the patient and the healthcare system, the better is the access.

Figure 1.2: The six dimensions of access

The six dimensions of access concept is based on the following publications:

Penchansky R, Thomas WJ. The concept of access: definition and relationship to consumer satisfaction. Medical Care. 1981; 19: 127-140.

Saurman E. Improving access: modifying Penchansky and Thomas's Theory of Access. Journal of Health Services Research & Policy. 2016; 21(1):36-39.

1.3.2 Access in terms of utilisation

Utilisation of medicines as a health need is described by Bradshaw (1972) in the 'Taxonomy of social need'. Bradshaw describes four categories of need: 'felt need, normative need, comparative need and expressed need.'

In access to medicines, the normative need relates to the healthcare system policies which determine which medicines are included in the drug formulary list. The felt need refers to the need recognised by the consumer after being prescribed or influenced to administer medicines. The expressed need corresponds to when the patient visits the pharmacy to obtain the medicine and the comparative need is linked to the capacity of the health system to provide an equitable response to the medical needs of the consumers (Soares, 2013; Vargas-Pelaez et al., 2017). Access to medicines results when all four perceptions of medicines as a health need coincide, if not, barriers to access medicines ensue.

1.3.3 Defining access

Saurman (2016) and Peters *et al*. (2018) state that 'Access enables a patient in need to receive the right care at the right time from the right provider and in the right place.' Access to medicines is achieved when the characteristics of consumers correspond to the aspects of the service such as location of pharmacies and cost of medicines (Whitehead, 1992). This ensures that individuals are capable to obtain medicines when facing the need for care.

1.4 Barriers to access medicines

Issues with access to medicines is a threat to the wellbeing of individuals. Barriers to access arise from factors related to the demand and the supply of medicines (Ensor and Cooper, 2004). Demand limitation factors affect the capability of people to access medicines while supply constraints are related to inefficiencies of the healthcare services. Bigdeli *et al.* (2013) categorised barriers to access medicines in five different levels of the health system: 'Individual level, health service delivery, health sector level, public policies, international and regional level.'

Barriers to access medicines at the individual level captures the demand from patients and their attitude to seek health services which depends on the social and cultural characteristics of the individual (Ensor and Cooper, 2004; Peters et al., 2008; Jacobs et al., 2012). The other levels encompass the access barriers related to the supply of medicines in the healthcare system. Health service delivery includes aspects related to the irregular availability and high prices of medicines, irrational prescribing, dispensing and quality of medicines. Barriers at the health sector level arise from the pharmaceutical governance functions including regulatory affairs, procurement and supply practices, inspections and post-marketing surveillance. Public policies at national level may influence trade, industry or legal sectors of the pharmaceutical industry. Barriers to medicines access in international markets incorporates pharmaceutical research and development, patents and intellectual property rights (Bigdeli et al., 2013).

1.4.1 Implications of major events on access to medicines

1.4.1.1 Brexit

The United Kingdom is a major centre for scientific research and the manufacture of medicines and medical devices. On 31 January 2020, the United Kingdom became a third country to the European Union (EU) and entered the transition period of Brexit[13]. Brexit has inflicted negative dynamic changes within the pharmaceutical sector impacting drug development, drug regulation and trans-European trade resulting in compromised accessibility (Song, 2016).

Major changes in the way medicines and medical devices are tested, analysed and regulated within the United Kingdom and European markets will result due to Brexit[14]. In the case of regulatory divergence, pharmaceutical corporations may have to follow separate approval procedures and meet different quality assurance criteria to obtain a marketing authorisation in the United Kingdom and the EU, leading to delays in timely access to medicines and repetition of clinical studies. Medicines may be held at borders and subject to rigorous time-consuming re-testing requirements that may significantly prolong processes and cause supply disruptions (Kazzazi et al., 2017; van Schalkwyk et al., 2019).

Before Brexit, 80% of the medicines supplied in Malta through the public and private sectors were sourced from the UK and Ireland since English is a secondary language in

[13] Edgington T. Brexit: What is the transition period? BBC. 2020 [cited 2020 May 20] Available from: URL: https://www.bbc.com/news/uk-politics-50838994

[14] Morgan P. The Brexit test: protecting pharmaceutical quality standards through better analysis. European Pharmaceutical Review. 2019 [cited 2020 May 20] Available from: URL: https://www.europeanpharmaceuticalreview.com/article/106670/the-brexit-test-protecting-pharmaceutical-quality-standards-through-better-analysis/

Malta[15]. The European Commission and the European Medicines Agency (EMA) have been working closely with EU Member States to guide and encourage pharmaceutical companies based in the United Kingdom to implement the necessary requirements to comply with EU law and ensure continuity of supply of medicines[16].

The regulatory preparedness required for marketing authorisations of medicines granted through national, decentralised and mutual recognition procedures before the Brexit withdrawal date include[17]:

i. UK marketing authorisation holders seeking to market their products in the EU must relocate to another Member State
ii. Batch release and testing must be carried out in an EU Member State
iii. UK Qualified Persons for pharmacovigilance must relocate to an EU Member State
iv. UK Pharmacovigilance System Master File must relocate to an EU Member State.

It is in the interest of the marketing authorisation holders to follow the necessary regulatory steps to continue to serve the needs of patients in the EU.

[15] Micallef A. What effect will Brexit have on the importation of medicines into Malta? TVM. 2019 [cited 2020 May 20] Available from: URL: https://www.tvm.com.mt/en/news/il-brexit-se-whatwhat-effect-will-brexit-have-on-the-importation-of-medicines-into-malta-affect-will-brexit-have-on-the-importation-of-medicines-into-malta-l-importazzjoni-tal-medicini-fmalta/

[16] European Medicines Agency. European authorities working to avoid shortages of medicines due to Brexit – questions and answers. 2020 [cited 2020 May 20] Available from: URL: https://www.ema.europa.eu/en/documents/other/european-authorities-working-avoid-shortages-medicines-due-brexit-questions-answers_en.pdf

[17] Malta Medicines Authority. BREXIT – Regulatory considerations. 2020 [cited 2020 May 20] Available from: URL: http://www.medicinesauthority.gov.mt/brexit?l=1

1.4.1.2 The coronavirus pandemic

The WHO declared the novel coronavirus (COVID-19) outbreak as a pandemic with a very high global risk of spread on 11 March 2020[18]. The COVID-19 pandemic has caused disruptive effects and placed enormous strain on the global supply of medicines.

The EU network has been observing closely the effects of the pandemic on the EU medicine supply chains. Lack of access to medicines may result from several pharmaceutical factors which include unavailability of the qualified personnel either because they cannot work from home or they are indirectly controlling the pandemic, lack of provision of active pharmaceutical ingredients required for the manufacturing of medicines which are mainly sourced from China and India where exports were restricted, financial problems encountered by different stakeholders, difficulties in the transportation of medicines from one country to another, increased demand for medicines used to treat COVID-19 patients and stockpiling by healthcare systems and consumers[19].

The EU Executive Steering Group on Shortages of Medicines Caused by Major Events was established to lead coordinated actions within the EU to prevent and mitigate disruptions in the supply of medicines and medical technologies[20]. Ongoing discussions aim to enhance the mechanisms for forecasting the future demand of medicines and

[18] World Health Organisation. WHO timeline – COVID-19. 2020 [cited 2020 Jun 26] Available from: URL: https://www.who.int/news-room/detail/27-04-2020-who-timeline---covid-19

[19] European Medicines Agency. Availability of medicines during COVID-19 pandemic. 2020 [cited 2020 Jun 26] Available from: URL: https://www.ema.europa.eu/en/human-regulatory/overview/public-health-threats/coronavirus-disease-covid-19/availability-medicines-during-covid-19-pandemic

[20] European Medicines Agency. EU authorities agree new measures to support availability of medicines used in the COVID-19 pandemic. 2020 [cited 2020 Jun 26] Available from: URL: https://www.ema.europa.eu/en/news/eu-authorities-agree-new-measures-support-availability-medicines-used-covid-19-pandemic

provide guidance on how to match the estimated demand with the available supply in order to ensure access to vital medicines[21].

The pharmaceutical industry has positively responded to the global need for action to treat COVID-19, from repurposing existing medicines, to developing vaccines, to searching for innovative ways to attack coronaviruses. Global access to effective vaccines and medicines is key to building herd immunity and eradicating the virus and free up beds in intensive care hospital wards[22]. The fight against the threat of COVID-19 is won when an approved vaccine or therapy would be accessible to all individuals.

1.5 Access to medicines – the Maltese scenario

Malta is a small island EU Member State which depends almost exclusively on imports of medicines and medical technologies which are supplied through the public and private markets[23]. The private pharmaceutical sector is made up of community pharmacies situated around Malta and Gozo which dispense medicines supplied through licensed pharmaceutical wholesalers.

[21] European Medicines Agency. EU actions to support availability of medicines during COVID-19 pandemic – update 7. 2020 [cited 2020 Jun 26] Available from: URL: https://www.ema.europa.eu/en/news/eu-actions-support-availability-medicines-during-covid-19-pandemic-update-7

[22] Edwards DJ. New products alone are not enough. Pharma can do more to halt COVID-19. Access to medicine foundation. 2020 [cited 2020 Jun 26] Available from: URL: https://accesstomedicinefoundation.org/media/uploads/downloads/5e95d85128fb9_ATMF_Viewpoint_Role_for_pharma_in_C-19_200414%20(1).pdf

[23] Grima IC. Cost containment in the pharmaceutical sector: the Maltese scenario. 2008 [cited 2020 May 20]. Available from: URL: file:///C:/Users/muscc156/Downloads/malta_de08.pdf

Medicines placed on the local public and private market are authorised by the Malta Medicines Authority (MMA) under the EU Directive 2001/83EC[24] and the Medicines Act Chapter 458[25]. The legislative framework safeguards public health by ensuring the quality, safety and efficacy of locally available medicines and that pharmaceutical activities are carried out according to the established standards of good practice[26].

1.5.1 The Maltese National Health Service

The Maltese National Health Service provides primary, secondary and tertiary health care services free of charge to all citizens. It is financed out of general taxation and there are no user charges, a system of co-payments or a reimbursement system (Azzopardi Muscat et al., 2017).

Primary health care in Malta is offered by public and private organisations that operate independently. There are seven public Health Centres in Malta that operate on a 24/7 basis offering various specialised services[27]. Health care coverage is complemented by the private hospitals and clinics. Secondary and tertiary care is mainly provided by

[24] European Commission. Directive 2001/83/EC of the European Parliament and of the Council on the community code relating to medicinal products for human use. 2001 [cited 2020 May 20]. Available from: URL: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

[25] Ministry for Justice, Culture and Local Government. Chapter 458 Medicines Act. Malta: The Ministry; 2003 [cited 2020 May 20]. Available from: URL: http://justiceservices.gov.mt/DownloadDocument.aspx?app=lom&itemid=8924&l=1

[26] Malta Medicines Authority. Introduction to medicines regulation. 2020 [cited 2020 May 20]. Available from: URL: http://www.medicinesauthority.gov.mt/introductionmedicinesregulation

[27] Cordina G, Borg A. Pensions, health and long-term care – Malta country document. Analytical support on social protection reforms and their socio-economic impact. 2014 [cited 2020 May 20]. Available from: URL: file:///C:/Users/muscc156/Downloads/MT_asisp_CD14.pdf

specialised public hospitals. Mater Dei Hospital is the principal teaching hospital that provides specialised, ambulatory, intensive care and inpatient care services (Azzopardi Muscat et al., 2017). On hospital discharge, all patients are given a free three-day medicine supply according to their prescription. If treatment needs to be continued, medicines must be bought through out-of-pocket payments.

1.5.1.1 Medicines entitlement

The Social Security Act Chapter 318 Article 23 and the Fifth Schedule (V) of the same Act entitle Maltese citizens to free medicines on the basis of the presence of disease[28]. Patients diagnosed with any condition listed in the legislation are entitled to the indicated free medicines which are available on the Government Formulary List (GFL)[29]. Non-entitled patients purchase medicines through out-of-pocket payments from private community pharmacies.

Free medicines may be entitled through the Second Schedule of the Social Security Act also known as the Pink Card on the basis of means as part of non-contributory benefits that provide social and medical assistance to patients with low income. For a patient to qualify for this entitlement, the Department of Social Security performs a means testing assessment. Patients with a Pink Card are only entitled to 'pink positive' medicines and medical devices as listed on the GFL which includes items for both acute and chronic use.

[28] Ministry for Justice, Culture and Local Government. Chapter 318 Social Security Act. Malta: The Ministry; 1987 [cited 2020 May 20]. Available from: URL: http://justiceservices.gov.mt/DownloadDocument.aspx?app=lom&itemid=8794

[29] Government of Malta. Pharmacy of Your Choice - Schedule V. 2019 [cited 2020 May 20]. Available from: URL: https://deputyprimeminister.gov.mt/en/poyc/Pages/360%C2%B0-One-Stop-Shop-Service-Concept/Medicines-Approval/Schedule-V.aspx

An 8-week supply of free medicines may be collected from the chosen community pharmacy registered under the Pharmacy of Your Choice (POYC) Scheme. A patient needs to visit the general practitioner or consultant specialist every 56 days for a clinical diagnosis and to have the medicine entitlement under the respective Schedule extended. To enhance patient care, all medical practitioners may change the dose of treatment for non-protocol regulated medicines since medicines prescribed for chronic conditions under the Schedule V Scheme require on-going monitoring.

1.5.1.2 The Maltese pharmaceutical procurement system

The Central Procurement and Supplies Unit (CPSU) is the entity responsible for the procurement of medicinal products, medical devices, works or services across the National Healthcare Services[30]. The CPSU operates in terms of an annual budget allocated by the central government to procure medicines and medical technologies available on the Government Formulary List.

The CPSU employs public procurement tendering procedures to ensure fairness in the acquisition of medicines and enable pharmaceutical economic operators to compete on an equal basis. Competition improves the financial sustainability of the health system by encouraging better quality and lower prices of medicines and medical technologies.

[30] Government of Malta. Central Procurement and Supplies Unit – Corporate identity. 2019 [cited 2020 May 20]. Available from: URL: https://deputyprimeminister.gov.mt/en/cpsu/Pages/About-Us/Corporate-Identity.aspx

1.6 Risk and access to medicine

Risk is the chance that any activity or action could happen and cause harm (Calman and Royston, 1997). Practically everything has an associated risk and there is no such thing as zero risk. Normally the benefits of an action should outweigh the risks.

In the field of medicine, risk modulates the occurrence of a disease and its prognosis in patients (Costa and Carneiro, 2011). On a daily basis, health care professionals are faced with decisions on risk where the benefit-risk ratio needs to be considered in the decision-making process (Conti et al., 2010).

Risk may be assessed and quantified through a structured approach to identify and understand risks associated with specific activities. Risk may be quantified using a three-dimensional approach by the Risk Triangle. The Risk Triangle considers three dimensions to risk; the probability of an event occurring and the severity of the consequences represented by two equal sides, and detectability of an adverse event before taking place which rests on the base of the triangle and has a shorter length. Detectability mitigates risk by reducing the probability of adverse events. It is not always given equal importance as probability and severity, but it should be considered for an accurate estimation of risk (Attard Pizzuto, 2016).

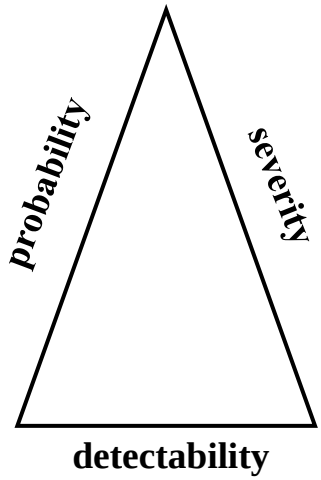

Figure 1.3: The Risk Triangle

Reproduced from: Attard Pizzuto M. Innovative Tools to Investigate Risk in Pharmaceutical Processes. 2016.

In access to medicines, risk to patients may be decreased by utilising drug intelligence to proactively address barriers to accessibility to minimise negative effects on the medicines needs of patients. The process involves recognising and defining the risk problem and its structural analysis followed by gathering necessary intelligence and selecting a course of action that minimises risk (Dickson, 2003).

1.7 Intelligence

Data, information and intelligence are essential attributes of the knowledge continuum to enable accurate decision-making and strategy[31]. The Data, Information, Knowledge and Wisdom (DIKW) hierarchy model explains the prerequisites for achieving intelligence (Shankar, 2017). Data is the lowest element of the DIKW pyramid which is a collection of outcomes and facts that is processed into information. Knowledge is structured and organised information developed through cognitive processing and validation. Wisdom represents the ability of people to solve problems and offer solutions through analysis by referring to information and past knowledge (Frické, 2009; Rowley, 2007).

Intelligence is incorporated in the DIKW model as an intermittent stage between knowledge and wisdom (Shankar, 2017). Intelligence is added value information that drives decisions towards goal-oriented functioning, flexibility, practical problem-solving and contextual intelligence[32]. Wisdom represents the human capabilities that involve reasoning, judgment, the application of creativity and intelligence.

[31] Roles B. The knowledge continuum: How data, information, and intelligence work together. 2020 [cited 2020 May 20] Available from: URL: https://www.introhive.com/resources/difference-between-data-information-intelligence/

[32] Durcevic S. Obtain business development with data intelligence tools & technologies. The datapine blog. 2019 [cited 2020 May 20] Available from: URL: https://www.datapine.com/blog/data-intelligence-and-information-intelligence-tools/

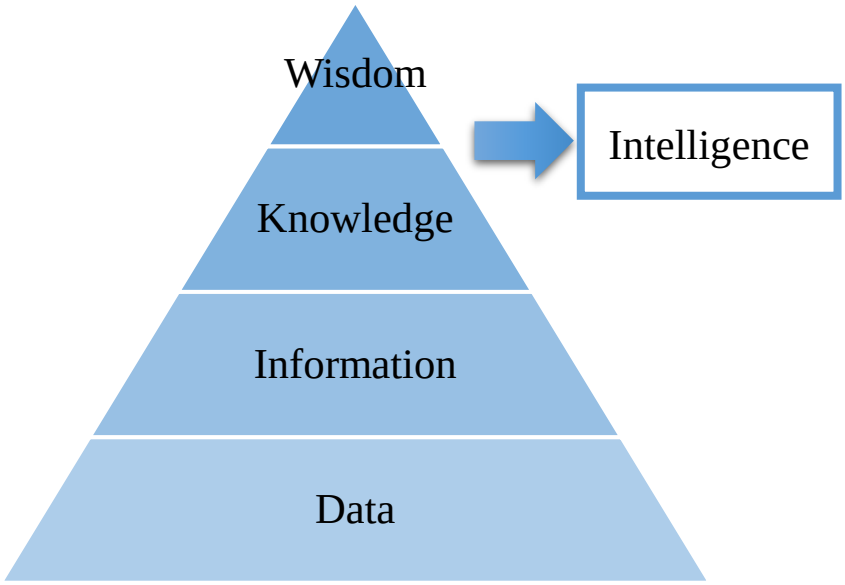

Figure 1.4: The DIKW Model incorporating intelligence in the hierarchy

Reproduced from: Shankar S. Looking into the Black Box: Holding Intelligent Agents Accountable. NUJS Law Review. 2017:10(451).

The art of intelligence transforms the 'what' and 'how' from information into the 'why' and 'when' of the decision-making process (Zeleny, 2005). The transformation is made through in-depth evaluation of data in the context of its source and reliability. Intelligence provides the necessary knowledge for effective management of resources and supports informed decision-making. With appropriate application, intelligence assists in generating strategic plans to deal with current issues and prepare for emerging problems[33].

[33] James L. Fail vs finished: The difference between information and intelligence. 2017 [cited 2020 May 20] Available from: URL: https://misti.com/infosec-insider/fail-vs-finished-the-difference-between-information-and-intelligence

1.7.1 Drug intelligence

In today's technological world, where big data and blockchain have changed the way data is analysed, it has become more important to apply intelligence to predict and find solutions in advance[34]. In the same way as criminal intelligence analysis permits law enforcement authorities to institute a pro-active response to crime (United Nations Office on Drugs and Crime, 2011), drug intelligence may be applied to dynamically address accessibility issues.

Offering the right treatment or taking the right action at the right time is critical in healthcare systems since there can be life or death consequences (Eggerth et al., 2019; Bahri, 2020). Authors emphasise that intelligence is a basic requirement for decision-making especially in the case of selection of medicines to consider questions of rationality, pharmacoeconomics, preparing for the needs of epidemics, preventive medicine and meeting the needs of the patient in developing a patient-centered environment (Skaria et al., 2020). Drug intelligence is generated through evaluation of data-driven findings and information and put into practice to enable efficient, strategic and operational decision making in healthcare systems. In the realm that decision-making must be done through intelligence and wisdom, the Medicines Intelligence and Access Unit at the Malta Medicines Authority was set up as a rationale for linking drug intelligence with access to medicines.

[34] Lebied M. 12 examples of big data analytics in healthcare that can save people. The datapine blog. 2018 [cited 2020 May 20] Available from: URL: https://www.datapine.com/blog/big-data-examples-in-healthcare/

1.8 Rationale for the research

Intelligence and access functions as related to medicines are multifactorial challenges which may have significant impact on public health and can contribute to health inequalities. Good collaboration, communication and coordinated actions from all stakeholders including patients, healthcare professionals and the pharmaceutical industry is essential to prevent and manage medicines access issues.

In Malta, the functions of the Medicines Intelligence and Access Unit within the Malta Medicines Authority have received acclamation to such an extent that responsibility was placed on the Unit to ensure that it operates in a scientifically structured manner. This forms the basis and the background for the rationale for this innovative research. The three pillars that concern the Malta Medicines Authority in its function as a guardian for the availability of medicines are safety, efficacy and quality.

An innovative framework driven by risk identification and medicines intelligence that moves towards a patient-centered personalised care approach was proposed to overcome the underlying causes of access issues and optimise patient health outcomes.

1.9 Research questions

The research investigates:

i. What are the access scenarios related to medicines?
ii. Which methods could be used to enhance access to safe, effective and good quality medicines?
iii. How could established methods in other areas of the regulatory sciences be adopted to assess the risk in taking actions and decisions to enhance access to medicines?

1.10 Aim and objectives

The research aimed to establish a scientific framework that provides a rational and prompt medicines accessibility strategy that meets the medicines needs of patients.

The objectives are to:

i. Retrospectively analyse queries related to access to medicines
ii. Propose a framework to deal with medicine access issues.

Chapter Two

Methodology

2.1 Overview

The research methodology consisted of 1. retrospective analysis of access issues recorded at the Medicines Intelligence and Access Unit (MIAU) and the establishment of a focus group to discuss barriers to access medicines and the risk imposed on the needs of patients. 2. A scientific framework was devised to sustainably enhance patient outcomes by acquiring medicines intelligence through processing of data-driven findings and information and through the analysis of real case scenarios.

2.2 Research Design

A pragmatic quantitative approach was adopted for the comprehensive extraction and systematic classification of retrospective data on accessibility issues. These were assessed by qualitative research methods by an expert panel in focus group discussions and evaluated through case scenarios. Risk identification and implications of access issues were the fundamental factors to develop a scientific framework to propose patient-centered best practices through medicines intelligence interventions.

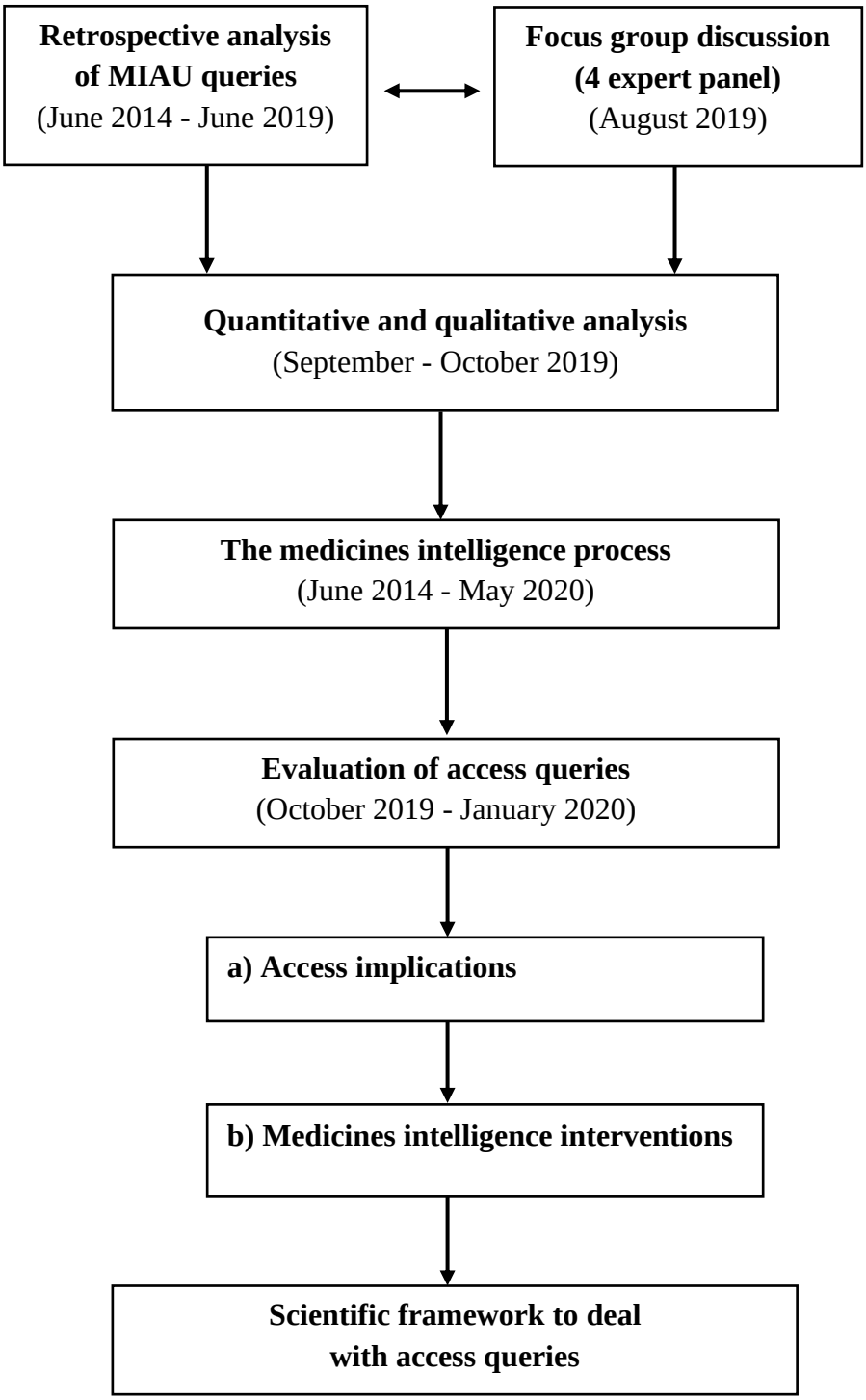

Figure 2.1: Flowchart of research methodology

2.3 Setting

The research was conducted at the Medicines Intelligence and Access Unit (MIAU) within the Malta Medicines Authority. The Malta Medicines Authority set up the MIAU in 2014 to address health and pharmaceutical concerns on an individual basis as part of the mission of the Malta Medicines Authority to protect and enhance public health through the regulation of medicinal products and pharmaceutical activities[35]. The MIAU facilitates access to medicines through the proactive compilation of drug intelligence and dialogue with stakeholders for the benefit of patients[36].

2.4 Ethics approval

An ethics approval from the University of Malta Research and Ethics Committee (UREC) was sought to conduct the research[37]. The UREC self-assessment form indicated that the research proposal required review of the Faculty Research Ethics Committee (FREC). An institutional approval to carry out the research at the Malta Medicines Authority was obtained from the Chairman and a data protection statement was signed. These were submitted to the FREC together with the research proposal and study protocol. The University of Malta Medicine and Surgery FREC granted ethical approval for the research, 'Drug intelligence and access to medicine' on 21 February 2020 following a presentation of the research proposal (Appendix 1).

[35] Malta Medicines Authority. Mission and Objectives. Malta: Malta Medicines Authority; 2020 [cited 2020 May 20]. Available from: URL: http://www.medicinesauthority.gov.mt/missionobjectives?l=1

[36] Malta Medicines Authority. Medicines Intelligence and Access Unit. Malta: Malta Medicines Authority; 2020 [cited 2020 May 10]. Available from: URL: http://www.medicinesauthority.gov.mt/directoratesunits?l=1#Medicines%20Intelligence%20and%20Access%20Unit

[37] University of Malta. Research Ethics & Data Protection – UM research. Malta: University of Malta; 2020 [cited 2020 May 10]. Available from: URL: https://www.um.edu.mt/research/ethics/forms

2.5 Retrospective analysis of access queries

Triangulation of data gathering from the MIAU and a focus group was used to gather robust, well-developed data and minimise bias.

2.5.1 Data extraction of MIAU queries

A retrospective analysis of all access queries recorded in the MIAU database over a 60-month period between June 2014 and June 2019 was carried out to extract and identify issues related to access medicines. Microsoft Excel® was used as a platform to document the date, description of the access query, action taken by the MIAU and outcome of the intervention. Issues related to access to medicines such as drug recalls, medicine safety notifications, pharmaceutical manufacturing issues and press conferences related to reduction in medicine prices were noted.

2.5.2 Focus group

The focus group was used as a tool to acquire knowledge and elicit qualitative data from prominent healthcare professionals. A four expert panel consisting of a general practitioner, a community pharmacist, a regulatory pharmacist and a clinical pharmacist was organised to scientifically discuss the data gathered from the retrospective analysis of MIAU queries and generate ideas for the purpose of devising recommendations to enhance access to medicine.

2.5.2.1 Focus group protocol

An electronic invitation was sent to the four healthcare professionals to confirm their availability to participate in a focus group to discuss access to medicines at the Malta Medicines Authority.

The focus group was led by a moderator who prompted a facilitated discussion and maintained a balanced input of participation from all members of the expert panel. The researcher followed the focus group and notes of the discussion outcomes were recorded in writing. The focus group protocol was adapted from Roberts *et al.* (1995) and included four main sections:

1. Introduction (Approximately 10 minutes)

   The expert panel were introduced and the moderator explained that the aims of the focus group discussion were to identify patient-related barriers to access, to analyse lack of access alongside patient medicines needs and to develop a risk-based scientific framework.

2. Rapport building stage (Approximately 10 minutes)

   A set of leading questions were prepared for the expert panel and used to guide the open discussion:

   a. What are the barriers to access medicines encountered in your practice?
   b. How do these barriers affect patient health outcomes?
   c. What are the risks imposed on the healthcare needs of the patient?
   d. How effective is the application of drug intelligence to enhance access to medicines?
   e. What measures do you recommend to optimise access to medicines?

3. In-depth discussion (Approximately 60 minutes)

   The moderator focused on the main questions and prompted an in-depth discussion to reveal the thoughts and ideas of the expert panel.

4. Closure (Approximately 10 minutes)

   The moderator provided a summary of the main outcomes of the discussion.

2.5.3 Quantitative and qualitative analysis

Quantitative and qualitative analysis was performed in line with the outcomes of the focus group. This involved:

1. Quantitative analysis of the access queries recorded at the MIAU through descriptive statistics by using Microsoft® Excel
2. Systematic categorisation of access queries according to the barriers to access medicines established in the focus group
3. Classification of MIAU queries according to the risk identified by the risk-based scientific framework developed in the focus group
4. Quantitative analysis of the determination of risk imposed by access issues on the patient medicines needs
5. Qualitative analysis of the MIAU access queries presenting the highest level of risk.

2.6 Development of the risk-based scientific framework

An innovative risk-based framework, designed to apply medicines intelligence to investigate access issues, was based on the evaluation of real case scenarios. A step by step guide was developed to clearly indicate the best practices which are recommended to proactively detect, address and mitigate access issues to the benefit of patients.

2.6.1 The medicines intelligence process

First-hand experience through active participation and observation of medicines intelligence processes was obtained while working at the MIAU. The process to acquire and implement medicines intelligence as a best practice involves continuous literature review and data analysis of the pharmaceutical sciences. This includes participation in local and European fora, specialised meetings, market research and educational development. Medicines intelligence is a valuable tool for problem-solving and decision-making since it offers added value information to drive patient-centered informed actions.

2.6.1.1 Literature review

A comprehensive literature search of peer-reviewed articles and scientific documents was conducted by applying Medical Subject Heading (MeSH) terms and relevant keywords such as access, health, patient-centered, accessibility, availability, affordability, adequacy, intelligence, medicines, risk, pharmaceutical care in PubMed®, HyDi Hybrid Discovery search gateway of the University of Malta and Google Scholar online literature databases. The snowball method (Wohlin, 2014; Badampudi et al., 2015) was adopted to expand the literature review with innovative aspects. Robust relevant documents on drug intelligence and accessibility to medicines were retrieved by applying backward and forward snowballing to the reference list of reviewed articles.

The legislative framework related to the accessibility of medicines was consulted. This includes EU Directive 2001/83EC[38] which was transposed in the Maltese legislation as the Medicines Act Chapter 458[39] of the Laws of Malta. Pertinent books, reports and dissertations were reviewed.

[38] European Commission. Directive 2001/83/EC of the European Parliament and of the Council on the community code relating to medicinal products for human use. 2001 [cited 2020 May 20]. Available from: URL: https://ec.europa.eu/health/sites/health/files/files/eudralex/vol-1/dir_2001_83_consol_2012/dir_2001_83_cons_2012_en.pdf

[39] Ministry for Justice, Culture and Local Government. Chapter 458 Medicines Act. Malta: The Ministry; 2003 [cited 2020 May 20]. Available from: URL: http://justiceservices.gov.mt/DownloadDocument.aspx?app=lom&itemid=8924&l=1

2.6.1.2 Observation

The approach adopted by the MIAU in handling access queries received through phone calls and e-mails from patients and healthcare professionals was observed from the start of the interaction to the end to assess patient centricity in enhancing access to medicines. The observation process involved monitoring of the verbal and written communication skills in addressing the access issues, cooperation with pharmaceutical stakeholders to sustain patient medicines needs, values, choices and provision of tailored advice on medicines access.

2.6.2 Real case scenarios

The access issues classified with the highest level of risk on the medicines needs of patients were categorised according to the rationale pertinent to the case and illustrated through real case scenarios. The case scenario method was adopted to conduct in-depth investigations of access issues in the everyday context in which they take place (Crowe et al., 2011).

Each real case scenario was described in three sections namely, case scenario description, access implications and medicines intelligence interventions (Table 2.2). The first section describes the background information of the real case scenario which gave rise to the respective access issue. The implications of lack of access on the medicines needs of patients were assessed in the second section of the case scenario. In the third section, a list of medicines intelligence interventions recommended by the MIAU were presented to rectify the access implications and enhance medicines access for the benefit of patients.

Table 2.2: Real case scenario sections

Section	Section title
1	Case scenario description
2	Access implications
3	Medicines intelligence interventions

Chapter Three

Results

3.1 Overview

The results consisted of 1. Retrospective analysis of the queries recorded on the Medicines Intelligence and Access Unit database and the outcomes of the focus group outlining the barriers of access to medicines and the risk imposed on the medicines needs of patients. 2. A description of the scientific framework through a step by step flowchart (Figure 3.4). This is based on medicines intelligence and the analysis of critical risk real case scenarios.

3.2 Results of retrospective analysis

Qualitative and quantitative analysis of 480 queries recorded through the MIAU over a 60-month period (June 2014 and June 2019) was conducted retrospectively to examine the challenges of access to medicines encountered by Maltese citizens.

3.2.1 Categorisation of MIAU queries

The 480 MIAU queries were systematically divided according to the rationale pertinent to the query in strategic categories as identified by the focus group. This resulted in four (4) barriers to accessing medicines:

1. Safety (n=201; 42%)
2. Availability (n=143; 30%)
3. Pharmacoeconomic (n=97; 23%)
4. Shortages (n=39; 8%)

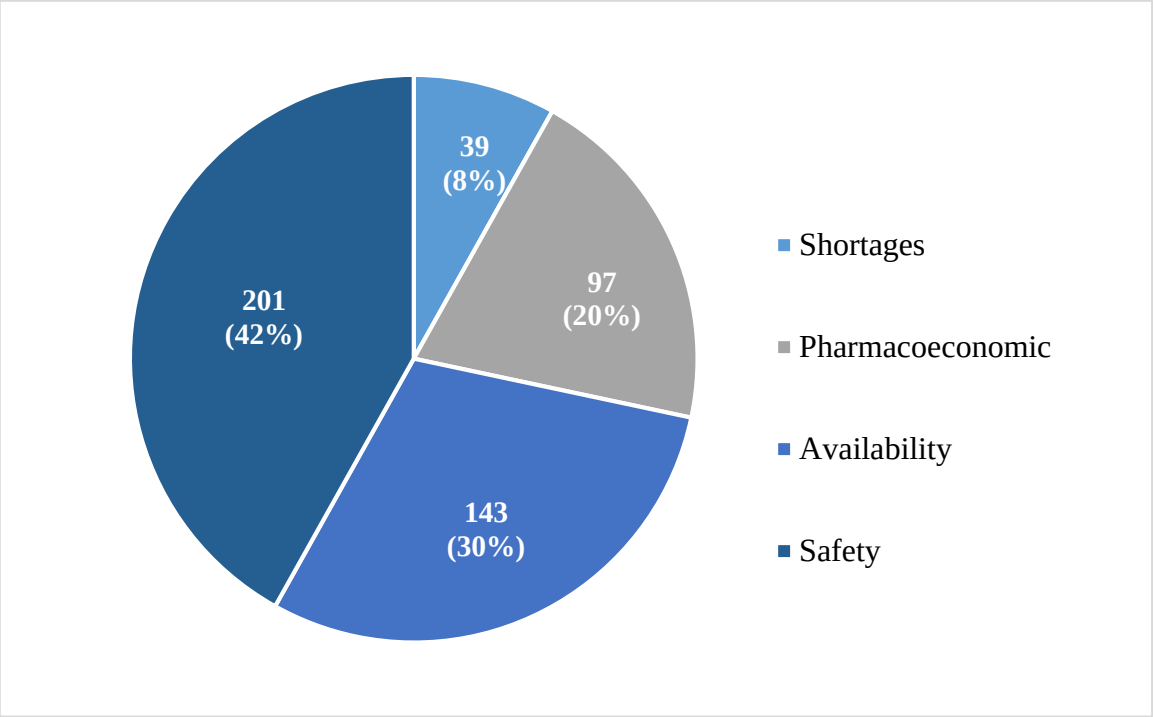

Figure 3.1: Systematic categorisation of MIAU queries (N=480)

3.2.2 Identification of risk

A risk-based approach was adopted to assess the implications of access issues on the medicines needs of patients. The focus group provided recommendations to classify risk by drawing on the classification of findings of the Good Manufacturing Practice quality management system and categorise risk as critical, major and other.

The focus group defined the criteria for classification of risk as:

- Critical

  The impact of the access issue may result in life threatening consequences or patient harm

- Major

  Access issues related to medicines cause patient inconvenience due to unavailability of the medicine or economic burden

- Other

  Access issues have no or little consequence

3.2.2.1 Risk classification of MIAU queries

The safety issues category presented the highest number of critical risk queries as 187 (93%) of the queries could have led to patient harm. Five per cent (n=10) imposed major risk since inconvenience was foisted on the medicines needs of the patient and 4 (2%) concerns related to the safety of medicines were classified as other risk.

Seven per cent (n=11) of queries categorised under availability issues were critical to the medical care of patients and 49% (n=70) of queries were of major risk since the prescribed medicines were not dispensed as they were not available to purchase from community

pharmacies or through the National Healthcare Service. Sixty-two (43%) queries were classified as other since there was no consequence on the medicines needs of patients and information was provided on how to access the medicine.

Access queries related to pharmacoeconomic issues showed the least critical risk (4%, n=4) when compared to other categories of access issues. Sixty-one per cent (n=59) were classified as major risk since the high cost of the medicine imposed economic burden on patients to obtain their medicines and 35% (n=34) were classified under other risk.

Forty-five per cent (n=17) of queries related to shortages of medicines were of critical risk since no alternative medicine was available and patients were left without treatment which could have led to life-threatening consequences. Twenty-two (56%) queries caused major risk on the medical needs of the patient since the prescribed medicine was changed to a suitable alternative medicine and no queries were classified as having other risk.

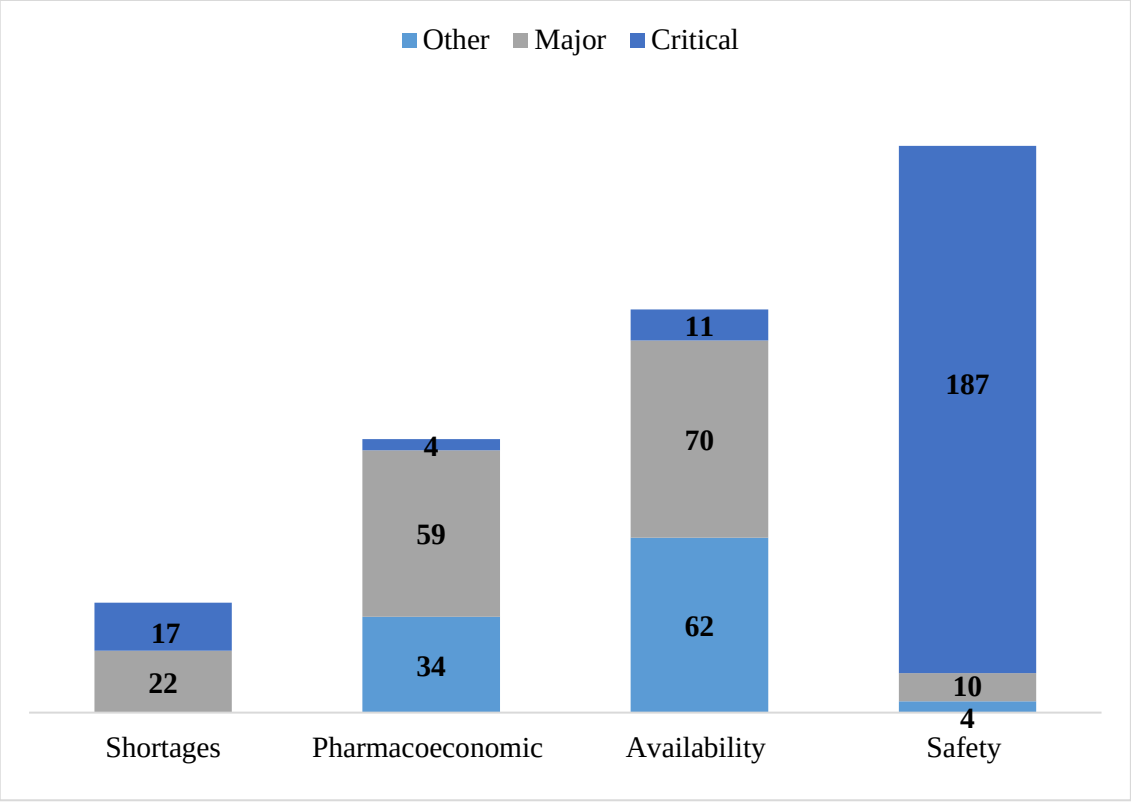

Figure 3.2: Risk classification of MIAU queries (N=480)

3.3 Scientific framework to deal with access issues

The research identified an innovative framework to deal with queries placed at the MIAU regarding access to medicines. The framework presents a step by step guide to address concerns by patients and healthcare professionals through medicines intelligence and a risk-based approach.

On receipt of the query, the pharmacist at the MIAU (Step 1) engages with the patient in an interactive dialogue based on active listening and open-ended questions to comprehend the issue and the challenges faced by the patient in accessing medicines. The query is documented on the MIAU database on Microsoft Excel®. The MIAU database of queries is continuously updated with the details of the access issue namely, the initial date when the query is received and the description of the query, which involves classification of the query under the category representing the barrier to access (availability, pharmacoeconomic, safety, shortages) and risk identification. The action taken, the medicines intelligence interventions and their outcomes on patient needs are noted for each query, including the date when the query is determined to be resolved.

Step 2 involves the identification of risk on the medicines needs of the patient by assessing the query in terms of the risk criteria established in the research, namely critical, major or other. In this way, queries are prioritised according to the implications on patient health outcomes and timely actions are taken. Queries with critical risk are given the most importance since repercussions of the access issue can be life-threatening or result in patient harm.

Step 3 assesses the implications imposed by the query on access to medicines. This clearly describes the access issues resulting from the query and directs the medicines intelligence process to support access to medicines.

Medicines intelligence is compiled through evaluation of knowledge obtained from research, seminars, scientific and technical groups, and direct information acquired from the patient. Medicines intelligence is an interactive process in the scientific framework that involves the application of the pharmacist expertise in ensuring that the medicines needs of patients are met. The pharmacist expertise and patient medicines needs are an integral part of the medicines intelligence process. These are depicted in parallelograms in Figure 3.4. Communication between the pharmacist and the patient is fundamental to achieve concordance with the proposed medicines intelligence interventions (Step 4).

Each query is different and requires a unique combination of communication and medicines intelligence interventions. The innovative scientific framework provides tailored recommendations to assist in added-value personalised care by supporting safe, effective, good quality and rational use of medicines.

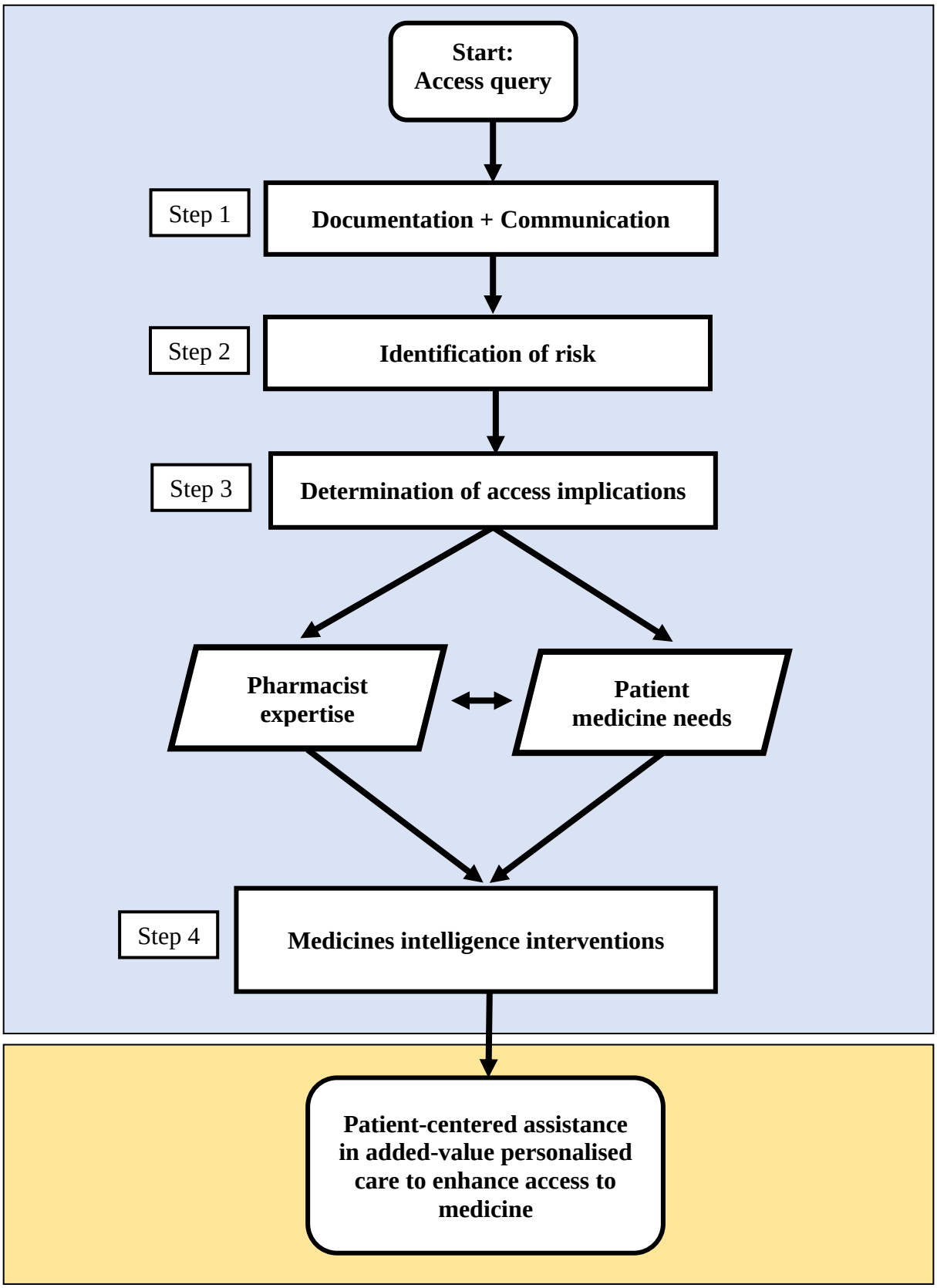

Figure 3.3: Schematic flow diagram of the risk-based scientific framework to address access issues

3.3.1 Medicines intelligence

Participation in fora provided the learning and networking opportunities to enhance the process of acquiring and providing intelligence and expertise in the area of access to medicine. The MIAU is a member of the:

- EU Executive Steering Group on Shortages of Medicines Caused by Major Events that leads coordinated actions to mitigate medicine supply disruptions
- European Single Point of Contact Network of the HMA/EMA Task Force on Availability of Authorised Medicines to obtain first-hand information on shortages and availability of centrally authorised and nationally authorised medicines
- Ad-hoc working group on 'Market Launch of Centrally Authorised Products' that considers the issues of accessibility and availability of the marketing of centrally authorised medicines
- Maltese Inter-Ministerial COVID-19 Task Force to safeguard public health
- Maltese Inter-Ministerial Taskforce on Brexit and availability of medicines

The researcher attended seminars and meetings held with diverse stakeholders in the pharmaceutical industry including the Superintendent of Public Health, the Ministry of Health, the CPSU, the POYC, wholesale distributors and EU entities. The knowledge and exposure obtained were of intrinsic importance to develop the necessary competencies for acquiring and providing medicines intelligence. Appendix 2 lists the seminars and conferences which were attended.

3.3.2 Evaluation of results of the critical risk queries

Two hundred and nineteen queries recorded at the MIAU were determined to be of critical risk to the medicines needs of patients and may lead to patient harm, fatalities and patients being left without the required medicines. Each category of the issues identified was analysed and evaluated to describe the cause of the issues leading to lack of access to medicines.

Seven real case scenarios were identified to have induced the access queries with critical risk. Critical risk imposed by safety issues was linked to adverse effects related to a change in the medicinal product manufacturer (n=12, 5.5%) and concerns associated with the contamination of active pharmaceutical ingredients with nitrosamine impurities (n=175, 79.9%). The was considered as an outlier since the access queries were associated with a disruptive occurrence in the pharmaceutical industry. Availability issues were critical when medicines were not marketed (n=8, 4%) or not listed on the Government Formulary List (n=3, 1.4%) and not dispensed through the National Healthcare Service. Shortages resulted in critical risk when there were disruptions in the supply chain (n=15, 6.8%) and withdrawal of the marketing authorisation of medicines (n=2, 0.9%) and alternative medicines were not readily available. Pharmacoeconomic issues presented critical risk to patients when medicines were not affordable due to high costs (n=4, 1.8%).

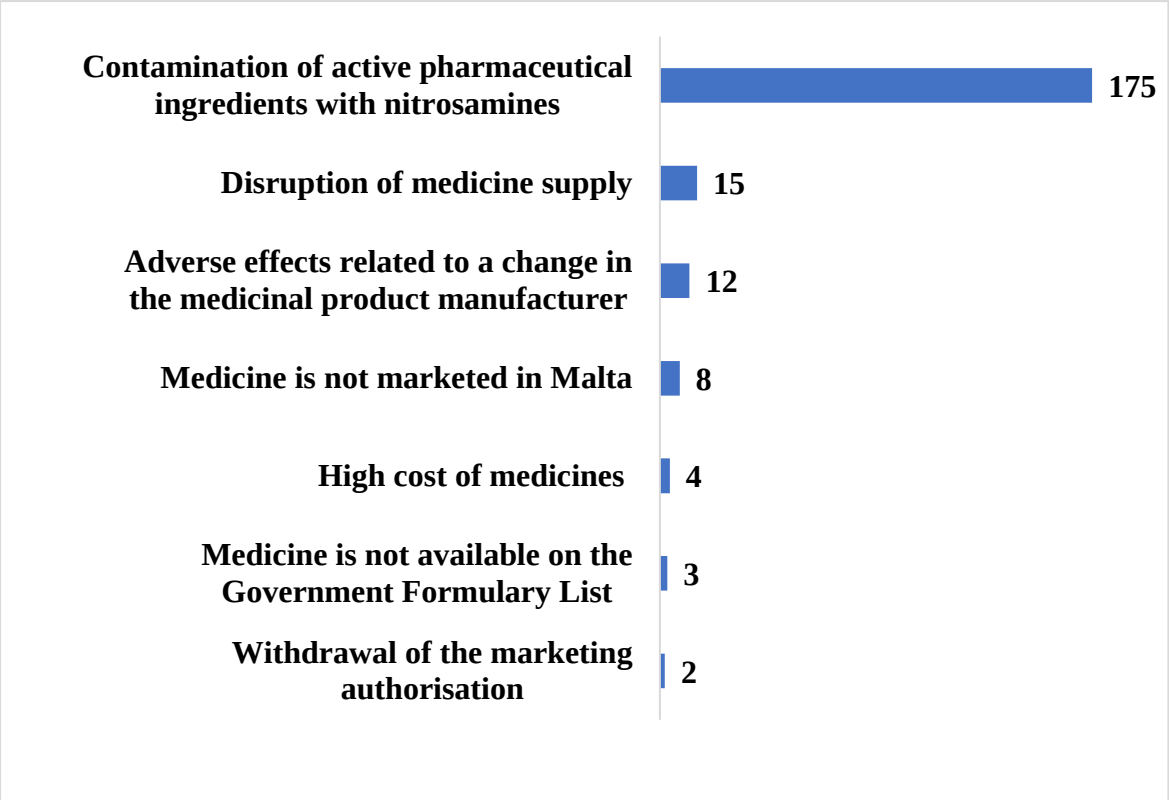

Figure 3.4: Real case scenarios of access queries with critical risk (N=219)

The resulting 7 real case scenarios depict the barriers to access medicines and pharmaceutical care which impose critical risk. These were evaluated by assessing the implications of access issues on patient medicines needs and proposing patient-centered medicines intelligence interventions to enhance access to medicines.

3.3.2.1 Case Scenario 1: Contamination of active pharmaceutical ingredients with nitrosamines

This case scenario presented the highest number of critical access queries at the MIAU. It was reported that a number of batches of valsartan-containing medicinal products from different manufactures were found to be produced from an active pharmaceutical ingredient contaminated with nitrosamine impurities. This created a massive shortage of valsartan-containing medicines and other alternative cardiovascular medicines since patients were prescribed and changed to alternative medicines.

3.3.2.1.1 Access implications

The presence of nitrosamines in medicines resulted in a global concern to patient safety. Access to these medicines was hindered due to drug recalls resulting in unavailability, lack of accessibility and inadequacy. Patient safety was compromised when patients on valsartan-containing medicines stopped abruptly the intake of valsartan resulting in unexpected cardiovascular problems such as stroke.

3.3.2.1.2 Medicines intelligence interventions

(1) A circular for healthcare professionals was published to advise patients not to stop valsartan abruptly.

(2) Valsartan-containing medicines were recalled when it was clear that quantities of an alternative medicine of valsartan was easily available.

(3) Wholesale distributors were contacted to supply alternative medicines to valsartan. A consignment of candesartan, an angiotensin receptor blocker was obtained.

(4) Awareness on the implications of the contamination of medicines with nitrosamines was raised among patients and healthcare professionals through the organisation of an interactive seminar.

3.3.2.2 Case Scenario 2: Disruption of medicine supply

Disruption may result due to manufacturing issues or as a consequence of pandemics leading to shortages of medicines and increased risk to public health. Example: Epipen® (adrenaline) autoinjectors which are used to treat anaphylaxis in emergency situations[40]. Adrenaline autoinjectors were in global shortage due to manufacturing issues.

3.3.2.2.1 Access implications

Disruption negatively affects medicine availability, accessibility and adequacy imposing critical risk on patient medicines needs. The shortage of Epipen® implicates a life-threatening risk on patients who experience anaphylaxis after inadvertent exposure to allergens.

3.3.2.2.2 Medicines intelligence interventions

(1) The expiry date of available Epipen® was extended for up to four (4) months in line with advice given by international experts and through evidence-based literature. If the solution is cloudy, the adrenaline auto-injector should be discarded.

[40] Electronic medicines compendium (EMC). Summary of product characteristics - Epipen® adrenaline 0.3mg auto-injector. 2019 [cited 2020 May 28] Available from: URL: https://www.medicines.org.uk/emc/product/5469

(2) Recommended healthcare professionals to prescribe and dispense only a maximum of two adrenaline autoinjectors per patient.

(3) Liaised with wholesale distributors to forecast demand and continuously stay on the lookout for stock of Epipen® or other adrenaline generics that may be sourced and supplied in Malta.

(4) Given the urgency and risk imposed by the shortage of Epipen®, the MIAU advised the Licensing Authority to approve requests to market adrenaline autoinjectors even though the package required relabelling. Circulars were sent to pharmacists to ensure that an English Patient Information Leaflet was dispensed with every pack.

(5) Facilities were structured at the Mater Dei hospital pharmacy in order to produce extemporaneously unit dose adrenaline in disposable syringes as an emergency measure. This operation was governed through the preparation of a Standard Operating Procedure.

3.3.2.3 Case Scenario 3: Adverse effects related to a change of the medicinal product manufacturer

The National Healthcare Service procures medicines according to the active pharmaceutical ingredient resulting in medicines which are supplied from different manufacturers. Changes from a proprietary medicinal product to a generic medicine may affect negatively patients stabilised on a specific medicine, often a proprietary product. Example: Patients who were stabilised on Concerta® (methylphenidate) prolonged-release tablets indicated for attention-deficit/hyperactivity disorder[41] experienced adverse effects and uncontrolled symptoms when they were transferred to the generic methylphenidate medicine.

3.3.2.3.1 Access implications

Lack of acceptability and inadequacy were the implications of access caused by changes from the proprietary medicine to the generic medicine resulting in adverse effects and inconvenience to the patient. Attention-deficit/hyperactivity disorder patients are difficult to stabilise because of the characteristic of the disease. In this case, psychiatrists found it difficult to determine if the uncontrolled symptoms were due to a case of relapse or a change in the product manufacturer.

[41] Malta Medicines Authority. Summary of product characteristics – Concerta® prolonged-release 18mg tablets. 2018 [cited 2020 May 28] Available from: URL: http://www.medicinesauthority.gov.mt/medicine-details?id=86268

3.3.2.3.2 Medicines intelligence interventions

(1) Awareness on adverse drug reaction reporting was raised to report adverse effects caused by medicines.

(2) Clinical studies were prompted to take place to assess the uncontrolled symptoms being experienced by the generic medicine as compared to the proprietary medicinal product.

(3) Action was taken with the supplier and the National Healthcare Service so that patients stabilised on Concerta® would remain on the proprietary medicine while new patients were started on the generic medicine.

3.3.2.4 Case Scenario 4: Medicine is not marketed in Malta

A medicine may not be marketed in Malta for a number of reasons: 1. The medicine is not registered, example Flixonase® (fluticasone) nasule drops indicated for the treatment of nasal polyps and associated symptoms of nasal obstruction[42]. 2. The medicinal product may be sourced but it is available in languages other than English or Maltese and relabelling expenses are not viable when considering the low demand in the Maltese market, example Visanne® (dienogest) tablets used in the treatment of endometrioses[43].

[42] Electronic medicines compendium (EMC). Summary of product characteristics – Flixonase® nasule drops. 2019 [cited 2020 May 28] Available from: URL: https://www.medicines.org.uk/emc/product/5503/smpc

[43] Malta Medicines Authority. Summary of product characteristics – Visanne® tablets. 2015 [cited 2020 May 28] Available from: URL: http://www.medicinesauthority.gov.mt/medicine-details?id=84693

3.3.2.4.1 Access implications

The resulting access implications of medicines which are not marketed in Malta include limitations related to availability, accessibility and adequacy. Availability is hindered since the medicine is not supplied by wholesale distributors and distributed to pharmacies resulting in lack of accessibility and inadequacy as patients cannot obtain the medicine at their convenience. Flixonase® nasule drops and Visanne® tablets are indicated for specific conditions and there is no direct alternative medicine available on the Maltese market.

3.3.2.4.2 Medicines intelligence interventions

(1) Wholesale distributors were contacted to source and supply Flixonase® nasule drops and Visanne® tablets to meet the patient medicines needs.

(2) In view that the medicines were needed for specific patients, the MIAU advised the Licensing Authority to approve the request to supply the unlicensed medicines; Flixonase® nasule drops and Visanne® tablets on a named patient basis for specific patients.

3.3.2.5 Case Scenario 5: High cost of medicines

Access queries regarding price of medicines in Malta being higher than in neighbouring countries or greater than the reference price data obtained from the Malta Competition and Consumer Affairs Authority. Examples: Queries related to the price of Xarelto® (rivaroxaban) anticoagulant tablets, Bexsero® (*Neisseria meningitidis* group B) vaccine, and Lyrica® (pregabalin) tablets indicated in neuropathic pain, epilepsy and generalised anxiety disorder[44].

3.3.2.5.1 Access implications

Pharmacoeconomic barriers limiting access to medicines result in lack of affordability and accessibility causing patients to be left without the required medicines. Xarelto® was not accessible because of the high consumer price. Patients who do not afford it used warfarin which has a cheaper price but necessitates compliance with regular international normalised ratio (INR) monitoring. If INR monitoring is missed, bleeding episodes may result.

Lyrica® (pregabalin) tablets is an originator medicine which was considered to be expensive. Patients often had to revert to alternative medicines which did not alleviate the symptoms of the respective conditions.

Bexsero® vaccine was launched on the private market with a high price resulting in individuals not affording to purchase and vaccinate against the bacteria *Neisseria meningitidis* group B which can lead to fatalities.

[44] Electronic medicines compendium (EMC). Summary of product characteristics – Lyrica® hard capsules. 2020 [cited 2020 May 28] Available from: URL: https://www.medicines.org.uk/emc/product/10303/smpc

3.3.2.5.2 Medicines intelligence interventions

(1) Liaised with the Malta Competition and Consumer Affairs Authority to obtain the reference price in other EU member states. Wholesale distributors were approached and requested to obtain a fair price for the Maltese market relative to the price sold in other countries.

(2) Investigated the possibility of sourcing the same medicine through parallel importations from countries where the price was cheaper than that sold in Malta such as Italy, Belgium and Greece. These medicines required over-labelling since the medicine package was not in the English language.

(3) Pharmaceutical wholesale distributors were encouraged to place generic medicinal products on the market to induce price competition. Several generic medicines of Lyrica® were introduced on the Maltese market resulting in price reduction of the originator medicine.

(4) Discussions with the health authorities and the Vaccine Committee in Malta were initiated to provide the Bexsero® vaccine to all children. This resulted in the inclusion of Bexsero® as part of the Government Immunisation Schedule making it available for free through the National Healthcare Service.

3.3.2.6 Case Scenario 6: Medicine is not available on the Government Formulary List

The Government Formulary List (GFL) includes a list of cost-effective medicines indicated for specific conditions which are supplied through the National Healthcare Service free of charge. Patients may be prescribed medicines which are not included in the GFL and they are only available on the private market. Examples: Combodart® (tamsulosin, dutasteride) combination medicinal product indicated in benign prostatic hypertrophy[45] and Galvus® (vildagliptin) indicated in type II diabetes mellitus[46].

3.3.2.6.1 Access implications

Lack of access of these medicines through the GFL results in financial burden on the patient who has to pay the full price of the medicine in order to access the prescribed treatment. This may result in non-compliance and complications of the respective medical condition.

3.3.2.6.2 Medicines intelligence interventions

(1) Recommendations were given to the Government Formulary List Advisory Committee to consider the inclusion of new medicines in the GFL. Galvus® (vildagliptin) was included in the GFL as part of a National strategy to control diabetes mellitus.

[45] Malta Medicines Authority. Summary of product characteristics - Combodart® hard capsules. 2019 [cited 2020 May 28] Available from: URL: http://www.medicinesauthority.gov.mt/medicine-details?id=84854

[46] Electronic medicines compendium (EMC). Summary of product characteristics – Galvus® tablets. 2018 [cited 2020 May 28] Available from: URL: https://www.medicines.org.uk/emc/product/6225

3.3.2.7 Case Scenario 7: Withdrawal of the marketing authorisation

The marketing authorisation of a medicinal product may be withdrawn by marketing authorisation holders or pharmaceutical companies due to marketing cessation or safety reasons. Brexit has caused the discontinuation of several medicines which originate from the UK affecting negatively the Maltese medicines supply chain. Examples of access queries related to medicines which were discontinued include Zoely® (nomegestrol, estradiol) oral contraceptive pill, Zovirax® (aciclovir) eye ointment used in the treatment of herpes simplex keratitis[47] and Palexia® (tapentadol) tablets indicated in the management of severe chronic pain[48].

3.3.2.7.1 Access implications

The discontinuation of medicines results in lack of accessibility, availability and inadequacy causing several repercussions on patient medicines needs including an increased risk of adverse effects related to the change in treatment. Awareness should be raised among patients to seek healthcare professional advice when changing medicines.

[47] Electronic medicines compendium (EMC). Summary of product characteristics - Zovirax® eye ointment. 2017 [cited 2020 May 28] Available from: URL: https://www.medicines.org.uk/emc/product/5469

[48] Electronic medicines compendium (EMC). Summary of product characteristics - Palexia® 100mg prolonged-release tablets. 2019 [cited 2020 May 28] Available from: URL: https://www.medicines.org.uk/emc/product/11410/smpc

3.3.2.7.2 Medicines intelligence interventions

(1) Wholesale distributors were contacted to source medicines containing the same active pharmaceutical ingredient/s and formulation as the medicines which were discontinued.

(2) Patients were referred to their clinician to discuss alternative medicines which were available on the market and may be prescribed for the respective condition.

3.4 Dissemination of results

An abstract titled *'Application of Drug Intelligence to Enhance Access to Medicine'* was accepted for poster presentation at the 79th International Pharmaceutical Federation World Congress of Pharmacy and Pharmaceutical Sciences, Abu Dhabi, United Arab Emirates and presented between the 22-26 September 2019 (Appendix 3).

Chapter Four

Discussion

4.1 Medicines intelligence to enhance access

The utopian scenario for access to medicine according to Bradshaw (1972) supports: Patients who would like to obtain a medicine (positive felt need) followed by the fact that the medicine is covered by the healthcare system formulary list (positive normative need) and when the patient presents at the pharmacy to collect the medicine (positive expressed need), the medicine is accessible and is supplied to the patient (positive comparative need).

While the concept of need as described by Bradshaw may be outdated, it has been found helpful to use the four steps described as fundamental basis to apply in the context of meeting patient medicines needs. In addition to other investigative and explorative areas of meeting the requirements of quality, safety and efficacy which are the pillars of any accessibility scenario. This research applies theoretical concepts to actual practice by considering a number of real case scenarios where intelligence combined with wisdom was applied as a best practice to recommend medicines intelligence interventions to enhance access to medicines. An analysis of the findings of this research point to the need of applying a scientific methodology to the justification of the procedures applied in meeting the medicines needs of patients.

The scientific logic was put in place in devising a framework to the activities of the Medicines Intelligence and Access Unit at the Malta Medicines Authority. A further thought in the development of this research which could be considered a limitation to the study or the next step in further research was the introduction of an algorithmic systemic

framework. This framework through the introduction of algorithms would fall in line with aspects of digitalisation. This research has exposed the cautions to be taken in adapting such a logic namely in that one is presented with the difficulty of an algorithm to fit the rationale behind the concepts exposed in this research namely how to align accessibility with personalised care and availability of personalised medicines. Scientific aspects such as point-of-care and pharmacogenetics have also to be taken into consideration but these fall outside the realm of this research.

As multiple dynamics and factors influence the pharmaceutical and health sectors, access continues to be a complex, multifaceted challenge which may lead to negative consequences on the patient health outcomes. The innovative scientific framework was formulated in such a way to proceed in line with the policy of the Malta Medicines Authority in the ration for establishing the Medicines Intelligence and Access Unit as a fundamental principle to move from regulatory affairs to regulatory sciences. The thesis provides relevance in adapting regulation in a patient-oriented manner while keeping within the legislation requirements. This has been exemplified through the real case scenarios which were resolved with the best practical methods keeping the patient at the centre of all activities. This contrasts with the traditional functions of a regulatory body to ensure that stakeholders abided by the legalistic aspects and not giving importance to the relevance of patient outcomes in terms of benefit to the patient and ensuring that the patient needs are met. Considering that the three pillars for regulatory sciences are quality, safety and efficacy, these pillars can only be optimally met if the patient is kept in the centre of all processes. This thesis attempted to put the patient in the centre of a regulatory

body taking into consideration the access to medicines as a primary function of the mission of the Maltese competent authority.

While disruption can negatively affect access to medicines such as the contamination of active pharmaceutical ingredients with genotoxic impurities, Brexit and the coronavirus pandemic, medicines intelligence may be successfully adopted to dynamically navigate challenges through informed decision-making and develop opportunities to safeguard patient medicines needs and wellbeing. It should be noted that while major events can have widespread risk, all access queries notwithstanding the level of risk are deemed significant to proceed with medicines intelligence interventions in a personalised-patient approach to ensure that the 'right patient receives the right medicine at the right time, in the right dose and through the right route' (Grissinger, 2010; Macdonald, 2010).

4.2 Strengths and limitations of the research

All access issues recorded in the Medicines Intelligence and Access Unit database were analysed. Selection bias was avoided since the queries were not selected through convenience sampling by the researcher.

A limitation of this research was that the focus group was conveniently selected and included four experts. Inclusion of a larger number of experts may have resulted in more robust discussions and recommendations to enhance access to medicine.

The research developed an innovative scientific framework to proactively address access issues through the application of medicines intelligence. A limitation of the research was that it did not evaluate the long-term patient health outcomes of the medicines intelligence interventions.

Another limitation of the research was that the data was not blinded. The researcher observed, investigated and conducted medicines intelligence interventions presented through the real case scenarios.

4.3 Recommendations

As a result of the research, it is recommended to implement the medicines intelligence risk-based approach as a best practice across other pharmaceutical services including the MMA quality management system in order to assess and take timely actions to resolve access issues for the benefit of patients.

Further studies are recommended to be performed to quantitatively measure the enhanced patient access to medicines and quality of life as a result of the implementation of the medicines intelligence risk-based approach to assess access issues.

Once the innovative scientific framework is implemented, it is proposed to perform a comparative study to investigate the timeliness in which access queries were resolved.

A research recommendation is to conduct surveys directed to consumers and healthcare professionals to identify and quantify the perception of people in accessing medicines and healthcare services.

It is recommended to organise interactive seminars directed to patients and health care professionals to raise awareness on the patient-centred functions of the MIAU in addressing access issues and assisting in patient specific added value medicines interventions.

It is proposed to extend the application of medicines intelligence to innovative aspects of the regulatory sciences including medical devices, cannabis for medicinal use and veterinary medicines.

4.4 Conclusions

Access to medicines has gained more importance globally in view of the ongoing disruptions. Medicines save lives and improve health outcomes when they are available, affordable, accessible, adequate, acceptable, accurate, of assured safety, efficacy and quality and used rationally.

The research identified the significance of a proactive personalised-patient approach to bridge the gap between patients and the regulatory and healthcare systems in order to enhance access to medicines. A scientific framework based on assessing access implications on patient health outcomes, obtaining and applying medicines intelligence in a risk-based approach was established as an innovative framework to detect, address and mitigate issues compromising access to medicines in order to provide a rational and prompt medicines accessibility strategy that meets patient needs. This provides a fundamental basis for robust contingency planning so healthcare systems are prepared for scenarios that may affect access to health, from patient perception of need to benefiting from the use of medicines. Caution should be taken when devising structured accessibility frameworks to allow ample room for interventions related to personalised care.

References

Ahmadiani S, Nikfar S. Challenges of access to medicine and the responsibility of pharmaceutical companies: a legal perspective. Daru Journal of Pharmaceutical Sciences. 2016;24(1):13-20.

Amisha, Malik P, Pathania M, Rathaur VK. Overview of artificial intelligence in medicine. Journal of Family Medicine and Primary Care. 2019;8(7):2328-2331.

Attard Pizzuto M. Innovative Tools to Investigate Risk in Pharmaceutical Processes. 2016.

Azzopardi Muscat N, Buttigieg S, Calleja N, Merkur S. Malta – Health system review. Health Systems in Transition. 2017;19(1):1-137.

Badampudi D, Wohlin C, Peterson K. Experiences from using snowballing and database searches in systematic literature studies. 19th International Conference on Evaluation and Assessment in Software Engineering - EASE '15. Nanjing, China. 2015:1-10.

Bahri P. Communicating about Risks and Safe Use of Medicines. Singapore: Springer Verlag; 2020.

Barei F. Value-added medicines: is there any room between market access challenges and "patient centricity"? International Journal of Pharmaceutical and Healthcare Marketing. 2018;12(1):71-76.

Bermudez J. Contemporary challenges on access to medicines: beyond the UNSG High-Level Panel. Ciênca & saúde coletiva. 2017;222 (8): 2435-2439.

Bigdeli M, Jacobs B, Tomson G, et al. Access to medicines from a health system perspective. Health Policy and Planning. 2013;28(7):692-704.

Bigdeli M, Shroff ZC, Godin I, Ghaffar A. Health systems research on access to medicines: unpacking challenges in implementing policies in the face of the epidemiological transition. The British Medical Journal Global Health. 2018; 2 Suppl 3:e000941.

Blenkinsopp A, Bond C, Raynor DK. Medication reviews. British Journal of Clinical Pharmacology. 2012;74(4):573-80.

Bradshaw J. The taxonomy of social need. In: McLachlan, G. (Ed.), Problems and Progress in Medical Care. Oxford University Press, Oxford. 1972.

Calman KC, Royston G. Personal paper: Risk language and dialects. British Medical Journal 1997;315:939-942.

Chatterjee JS. From compliance to concordance in diabetes. Journal of Medical Ethics 2006; 32:507-510.

Conti AA, Conti A, Gensini GF. The concept of risk in medicine: historical and epistemological reflections. Minerva Med. 2010;101(1):59-62.

Costa J, Carneiro AV. Calculation, expression and perception of risk in medicine: implications for clinical decision-making. Portuguese Journal of Cardiology. 2011;30(1):95-119.

Cousin G, Schmid Mast M, Roter DL, Hall JA. Concordance between physician communication style and patient attitudes predicts patient satisfaction. Patient Education and Counseling. 2012; 87(2):193-197.

Crowe S, Cresswell K, Robertson A, Huby G, Avery A, Sheikh A. The case study approach. BMC Medical Research Methodology. 2011; 11:100.

Cushing A, Metcalfe R. Optimizing medicines management: From compliance to concordance. Therapeutics and Clinical Risk Management. 2007;3(6):1047-1058.

Dégardin K, Roggo Y, Margot P. Forensic intelligence for medicine anti-counterfeiting. Forensic Science International. 2015;248:15-32.

Duong MH, Moles RJ, Chaar B, Chen TF. Stakeholder perspectives on the challenges surrounding management and supply of essential medicines. International Journal of Clinical Pharmacy. 2019;41(5):1210-1219.

Durrani H. Healthcare and healthcare systems: inspiring progress and future prospects. mHealth 2016;2:3-12.

Eggerth A, Hayn D, Schreier G. Medication management needs information and communications technology-based approaches, including telehealth and artificial intelligence. British Journal of Clinical Pharmacology. 2019;1-8.

Ellul IC. Brexit : the pharma industry & Malta's availability of medicines. The Synapse. 2016; 15(2):3

Ensor T, Cooper S. Overcoming barriers to health service access: influencing the demand side. Health Policy and Planning. 2004;19:69–79.

Ferrario A, Humbert T, Kanavos P, Pedersen HB. Strategic procurement and international collaboration to improve access to medicines. Bulletin of the World Health Organisation. 2017;95(10):720-722.

Fleming A. On the antibacterial action of cultures of a penicillium, with special reference to their isolation of *B.Influenzae*. The British Journal of Experimental Pathology. 1929; X:226.

Fotaki M. Patient choice and equity in the British National Health Service: towards developing an alternative framework. Sociology of Health & Illness. 2010; 32(6): 898-913.

Frické M. The knowledge pyramid: the DIKW hierarchy. Journal of Information Science. 2009;35(2):131-142.

Gannedahl, M, Udechuku A, Bending MW. Initiatives driving accelerated access to medicines in Europe: Review of recent concepts and developments. Medicine Access @ Point of Care. 2018; 1-7.

Goodson JD. Patient protection and affordable care Act: Promise and peril for primary care. Annals of Internal Medicine. 2010; 152(11):742-744.

Grammaticos PC, Diamantis A. Useful known and unknown views of the father of modern medicine, Hippocrates and his teacher Democritus. Hellenic Journal of Nuclear Medicine. 2008;11(1):2-4.

Grissinger M. The Five Rights: A Destination Without a Map. P&T: a peer-reviewed journal for formulary management. 2010;35(10):542.

Hajar R. History of medicine timeline. Heart Views. 2015;16(1):43-45. doi:10.4103/1995-705x.153008

Hohl CM, McGrail K, Sobolev B. The effect of pharmacist-led medication review in high-risk patients in the emergency department: an evaluation protocol. CMAJ Open. 2015;3(1):103-110.

Huiskes VJ, Burger DM, Van den Ende CH, Van den Bemt BJ. Effectiveness of medication review: a systematic review and meta-analysis of randomized controlled trials. BioMed Central Family Practice. 2017;18(1):5.

Jacobs B, Ir P, Bigdeli M, Annear PL, Van Damme W. Addressing access barriers to health services for the poor: an analytical framework for selecting appropriate interventions in low income countries. Health Policy and Planning. 2012;27:288–300.

Jones J, Cronin JM. The pros and cons of formularies. Journal of Managed Care Pharmacy. 2000; 6(3):203-207.

Kazzazi F, Pollard C, Tern P, Ayuso-Garcia A, Gillespie J, Thomsen I. Evaluating the impact of Brexit on the pharmaceutical industry. Journal of pharmaceutical policy and practice. 2017;10:32.

Krueger RA. Focus Groups: A Practical Guide for Applied Research 3rd edition. California: Sage; 2000.

Levesque JF, Harris MF, Russell G. Patient-centred access to health care: conceptualising access at the interface of health systems and populations. International Journal for Equity in Health. 2013;12:18.

Macdonald M. Patient safety: Examining the adequacy of the 5 rights of medication administration. Clinical nurse specialist. 2010; 24(4):196-201.

Manikandan S. Are we moving towards a new definition of essential medicines? Journal of Pharmacology & Pharmacotherapeutics. 2015;6(3):123-125.

McLaughlin CG, Wyszewianski L. Access to care: remembering old lessons. Health Services Research. 2002;37(6):1441-1443.

Morgan S, Hanley G, Greyson D. Comparison of tiered formularies and reference pricing policies: a systematic review. Open Medicine. 2009;3(3):131-139.

Murray M. Access to health services to reduce morbidity and mortality. International Journal of Childbirth. 2018;8(4):212-214.

Nyumba TO, Wilson K, Derrick CJ, Mukherjee N. The use of focus group discussion methodology: Insights from two decades of application in conservation. Methods in Ecology and Evolution. 2018;9:20-32.

Ojiako U, Chipulu M, Karatas-Ozkan M, Siao M, Maguire S. Intelligence management opportunities for SMEs. Journal of Small Business and Enterprise Development. 2015; 22(4):698-715.

Penchansky R, Thomas WJ. The concept of access: definition and relationship to consumer satisfaction. Medical Care. 1981; 19: 127-140.

Peters DH, Garg A, Bloom G et al. Poverty and access to health care in developing countries. Annals of the New York Academy of Sciences. 2008;1136:161–71.

Rosenfeld CR. Insulin therapy in type 2 diabetes mellitus: history drives patient care toward a better future. The Journal of the American Osteopathic Association. 2013;113(4 Suppl 2):S4-S5.

Rowley J. The wisdom hierarchy: representations of the DIKW hierarchy. Journal of Information Science. 2007; 33(2):163-180.

Saurman E. Improving access: modifying Penchansky and Thomas's Theory of Access. Journal of Health Services Research & Policy. 2016; 21(1):36-39.

Skaria R, Satam P, Khalpey Z. Opportunities and challenges of disruptive innovation in medicine using artificial intelligence. The American Journal of Medicine. 2020;133(6):e215-e217.

Smith B. No-deal Brexit could impact medicine supplies, NAO warns. Civil Service World. 2019.

Song CH. Understanding the Aftermath of Brexit: Implications for the Pharmaceutical Industry. Pharmaceutical Medicine. 2016; 10;30(5):253-256.

United Nations General Assembly. International Covenant on Economic, Social and Cultural Rights. United Nations Treaty Series. 1966; 993:3.

United Nations General Assembly. Universal Declaration of Human Rights. 1948; 217 A (III).

United Nations Office on Drugs and Crime. Criminal intelligence: Manual for analysts. New York: United Nations Office; 2011.

Van Rossum A, Holsopple M, Karpinski J, Dow J. The missing link: Evolving accessibility to formulary-related information. Pharmacy and Therapeutics. 2016;41(11):698-725.

van Schalkwyk MCI, Barlow P, Stuckler D, Rae M, Lang T, Hervey T, Mckee. Assessing the health effects of "no deal" Brexit. British Medical Journal. 2019; 366: l5300.

Vargas-Pelaez CM, Soares L, Rover MR, Blatt CR, Mantel-Teeuwisse A, Rossi Buenaventura FA, et al. Towards a theoretical model on medicines as a health need. Social Science & Medicine. 2017; 178:167–74.

Wahlster P, Scahill S, Lu CY, Babar Z. Barriers to access and use of high cost medicines: A review. Health Policy and Technology. 2015; 4(3): 191-214.

Whitehead M. The concepts and principles of equity and health. International Journal of Health Services. 1992; 22:429–445.

Wohlin C. Guidelines for snowballing in systematic literature studies and a replication in software engineering. 18th International Conference on Evaluation and Assessment in Software Engineering - EASE '14. New York, USA. 2014:38:1–38:10.

Woodhouse KW. Drug formularies--good or evil? The clinical perspective. Cardiology. 1994;85 Suppl 1:36-40.

World Health Organisation. Constitution of the World Health Organisation. American Journal of Public Health. 1946; 36(11):1315-1323.

Yuan H, Ma Q, Ye L, Piao G. The traditional medicine and modern medicine from natural products. Molecules. 2016;21(5):559.

Zeleny M. Knowledge-information autopoietic cycle: towards the wisdom systems. International Journal of Management and Decision Making. 2005;7(1):3-18.

Appendix 1

The University of Malta Medicine and Surgery

Faculty Research Ethics Committee ethical approval

L-Università ta' Malta

Faculty of
Medicine & Surgery

University of Malta
Msida MSD 2080, Malta

Tel: +356 2340 1879/1891/1167
umms@um.edu.mt

www.um.edu.mt/ms

Ref No: FRECMDS_1819_136

Monday 24 February 2020

Ms Caroline Muscat
95, Roseville,
St. Peter Street,
Mgarr. MGR1544

Dear Ms Muscat,

Please refer to your application submitted to the Faculty Research Ethics Committee in connection with your research entitled:

Drug intelligence and access to medicine

The Faculty Research Ethics Committee granted ethical approval for the above mentioned application during the meeting held on 21 February 2020.

Yours sincerely,

Professor Pierre Mallia
Chairman
Research Ethics Committee

Appendix 2

List of seminars and conferences attended

3 February 2020	The Novel Coronavirus – Seminar for healthcare professionals Health Promotion and Disease Prevention Directorate in collaboration with the Malta Medicines Authority and the Academy for Patient-centered Excellence and Innovation in Regulatory Sciences
9 October 2019	Implications of cannabis for medicinal purposes Networking meeting led by Professor Jorge Manzanares Robles Malta Medicines Authority
22 -26 September 2019	New horizons for pharmacy – Navigating the winds of change 79th International Pharmaceutical Federation World Congress of Pharmacy and Pharmaceutical Sciences Abu Dhabi, United Arab Emirates
19 – 21 June 2019	96th Heads of Medicines Agencies Meeting Bucharest, Romania
29 – 30 May 2019	Regulatory sciences as applicable to cannabis for medicinal and research purposes Networking meeting Malta Medicines Authority in collaboration with the Organisation for Professionals in Regulatory Affairs

15 March 2019	11th Meeting of the European Commission Expert Group on Safe and Timely Access to Medicines for Patients Brussels, Belgium
28 February 2019	Digitalisation in Healthcare and its challenges for the pharmaceutical profession – Continuous professional development as a tool to foster e-health learning for patient-centred care European Pharmaceutical Student Association Annual Reception 2019, European Parliament, Brussels, Belgium
20 – 22 February 2019	95th Heads of Medicines Agencies Meeting Timisoara, Romania
3 December 2018	10th Meeting of the European Commission Expert Group on Safe and Timely Access to Medicines for Patients Brussels, Belgium
28 - 30 November 2018	Facing the challenges: Equity, Sustainability and Access INFARMED, Lisbon, Portugal
20 – 21 November 2018	Medical Cannabis World Forum 2018 Valletta, Malta

8 - 9 November 2018	HMA/EMA workshop on availability of authorised medicines European Medicines Agency, London, United Kingdom
7 November 2018	Bilateral discussions on medical devices and Brexit at the Medicines and Healthcare products Regulatory Agency London, United Kingdom
25 July 2018	The Valsartan Saga: Science, Myths, Realities Seminar led by Professor Anthony Serracino Inglott Malta Medicines Authority in collaboration with the Superintendence of Public Health and the Department of Pharmacy at the University of Malta
18 July 2018	Biosimilars: The importance of non-proprietary names Seminar led by Professor Philip Schneider The Department of Pharmacy at the University of Malta in collaboration with the Malta Medicines Authority and the Malta Pharmaceutical Association
17 July 2018	Training LI022/03 – Processing of applications for Marketing Authorisations submitted through the Decentralised Procedure with Malta as a Reference Member State Malta Medicines Authority

24 April 2018	Empowering pharmacists to evaluate and ensure access to innovative medicines workshop 41st European Pharmaceutical Student Association Annual Congress, Baarlo, the Netherlands
13-14 March 2018	Training: Introduction to EU Regulatory Procedures Malta Medicines Authority in collaboration with the Organisation for Professionals in Regulatory Affairs
12 March 2018	Training: Essentials of EU Regulatory Affairs Malta Medicines Authority in collaboration with the Organisation for Professionals in Regulatory Affairs
27 January 2017	European Integration, Small States and Access to Medicines workshop University of Malta in collaboration with Small States and Health

Appendix 3

Dissemination of results in international fora

Abstract accepted for poster presentation at the 79th International Pharmaceutical Federation World Congress of Pharmacy and Pharmaceutical Sciences, Abu Dhabi, United Arab Emirates, September 2019

APPLICATION OF DRUG INTELLIGENCE TO ENHANCE ACCESS TO MEDICINE

Caroline Muscat[1,2], Annalise Attard[1,2], Anthony Serracino-Inglott[1,2]

[1]Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta, Msida, Malta

[2]Malta Medicines Authority, Malta Life Sciences Park, San Ġwann, Malta

Background

Access to medicine and the continuous supply of affordable medicines with adequate quality, safety and efficacy are principal pillars of an effective health system.

Purpose

To investigate an innovative approach to enhance the accessibility to medicines through the compilation and practical application of drug intelligence. The objective of the study is to develop a system that provides a rational and prompt therapeutic strategy for the right individual at the right time.

Method

A retrospective and prospective gathering of medical events recorded at the Medicines Intelligence and Access Unit within the Malta Medicines Authority is carried out. Quantitative and qualitative analysis is performed. The intelligence gathered is validated through focus groups consisting of a general practitioner and two pharmacists from the community pharmacy and the pharmaceutical industry. The outcomes are adopted to draft, validate and implement a standard operating procedure to sustainably enhance patient outcomes.

Results

The systematic classification and evaluation of the rationale pertinent to the medical event was conducted to obtain intelligence on accessibility issues such as pharmacoeconomic aspects, drug shortages, falsified medicines, drug recalls, health technology assessments and use of generic versus branded medicines. The implication of threats, opportunities and outcomes on the medical needs of 50 patients posed by accessibility issues was addressed with 56 resolved cases.

Conclusion

The development of a proactive approach to assist in patient specific added value therapeutic interventions allows better informed medical decisions, enhanced health outcomes and improved access to medicines that meets patient needs.

L-Università ta' Malta | Faculty of Medicine & Surgery | Department of Pharmacy

APPLICATION OF DRUG INTELLIGENCE TO ENHANCE ACCESS TO MEDICINES

Caroline Muscat[1,2], Annalise Attard[1,2], Anthony Serracino Inglott[1,2]

[1]Department of Pharmacy, Faculty of Medicine and Surgery, University of Malta, Msida, Malta

[2]Malta Medicines Authority, San Gwann, Malta

Email: caroline.g.muscat@gov.mt

INTRODUCTION

Access to medicines and the continuous supply of affordable medicines with adequate quality, safety and efficacy are principal pillars of an effective health system. This is an evolving, complex and multifaceted challenge that requires coordinated actions from all stakeholders[1].

AIM

1. To gather information on medical events related to accessibility to medicines
2. Apply the knowledge and intelligence gathered to assist in meeting the personal medical needs of the patient

METHOD

Retrospective gathering of medical events recorded at Medicines Intelligence and Access Unit within the Malta Medicines Authority → Quantitative and Qualitative analysis of the data collected → Validation of the intelligence gathered through a focus group → Assessment of the implication of threats, opportunities and outcomes on the medical needs of the patient

RESULTS

Fifty six medical events were recorded between January and May 2019 on the Medicines Intelligence and Access Unit database. These were systematically classified and evaluated according to the rationale pertinent to the medical event *(Figure 1)*.

The data gathered from each medical event was assessed and the implication of threats, opportunities and outcomes on the medical needs of each patient concerned was identified. The intelligence obtained was used to sustainably enhance patient therapeutic care outcomes.

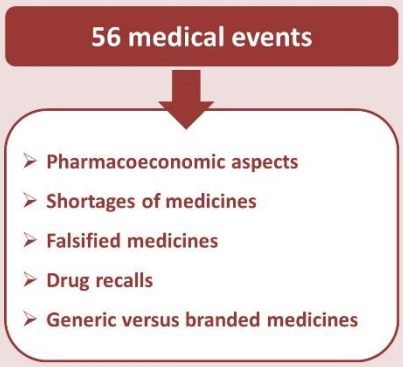

Figure 1:
Classification categories of the medical events

CONCLUSION

Drug intelligence is a supporting tool to provide an objective and integrated solution to measure and optimise the therapeutic needs of patients. It is concluded that patient specific added value therapeutic interventions allow better informed medical decisions, enhanced health outcomes and improved access to medicines that meet patient needs.

REFERENCES

[1] Wahlster P, Scahill S, Lu CY, Babar Z. Barriers to access and use of high cost medicines: A review. Health Policy and Technology. 2015; 4(3): 191-214.