A Review of the

POYC Medicines Approval System

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of the requirements of the

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To my family

Gina, Mandy, Allen, Ellen, Ocer, Ely, and Daryl

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Abstract

The Pharmacy of Your Choice (POYC) is the government's pharmaceutical service responsible for approving free medicine entitlements under the Schedule V legislation. According to the 2013 Annual Report, 50,251 applications were processed and 3,184 out of the 21,168 requests for protocol-regulated items were not approved due to failure to follow set protocols as per the Government Formulary List (GFL). With the increasing number of applications and non-approvals of medicine entitlements resulting in the delay of access to medicines, this research aimed to optimise the POYC medicines approval system through pharmacist interventions to ensure efficient service delivery to patients. A mixed-method three-phased development design was utilised. The reasons for non-approvals before and during the COVID-19 pandemic were characterised through retrospective database review and Pareto analysis. A panel composed of one community pharmacist, one prescribing doctor, and two POYC officers evaluated non-approval risks through Failure Mode and Effects Analysis (FMEA) via Delphi technique using expert-agreed risk matrix and five-point ordinal scales for severity, occurrence, and detectability to develop interventions to streamline access to entitlement approvals. From January 2012 to October 2020, characterisation of medicines not approved (n=26,785) showed that the top medicines contributing to non-approvals were clopidogrel (8%), levothyroxine (5%), and omeprazole (4%). Process-specific reasons which served as bottlenecks were: medicine not corresponding to the Schedule V condition (43%), application not according to government protocol (10%), and medicine not available on the GFL (7%). Research panelists agreed that the potential failure modes in order of criticality requiring interventions were: application was not according to government protocol, medicine did not correspond to Schedule V

condition, application was awaiting for approval for exceptional cases, foreign patients failed to bring supporting documents to confirm eligibility to Schedule V scheme, and wrong prescriber criteria. Interventions identified in the study to mitigate risks in the medicines approval system included: orientation manual for applying prescribers and participating pharmacies, review of information technology systems to facilitate access to supporting documents, and monthly feedback system regarding data on non-approvals. Risk assessment and prioritisation of the most common causes of non-approvals through FMEA as a regular quality exercise is important to identify interventions or optimisation of processes which can reduce delays in access to entitlement approvals and enhance a patient-centric approach.

Keywords: chronic conditions; pharmacist interventions; medicines entitlement; formulary; FMEA

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Glossary of Terms as Applicable to POYC Setting

Detectability

Operationally-defined as the degree to which the potential failure mode may be observed or recognised using a five-point ordinal scale based on the Schedule V application procedure

Failure Mode and Effects Analysis (FMEA)

Systematic and pro-active approach of evaluating potential failure modes in a process[1]

Foreign Patients Applications

Operationally-defined as Schedule V applications of foreign patients initially not processed due to unavailability of supporting documents to prove eligibility to the Schedule V scheme

Full Non-approval

Operationally-defined as Schedule V applications in which all items in the application form were not approved (for example, both clopidogrel and omeprazole were not approved for an application submitted for both clopidogrel and omeprazole under the Ischaemic Heart Disease Schedule V condition)

[1] Institute for Healthcare Improvement. Risk Priority Number (from Failure Modes and Effects Analysis) [Internet]. IHI; 2021 [cited 2021 May 14]. Available from URL: http://www.ihi.org/resources/Pages/Measures/RiskPriorityNumberfromFailureModesandEffectsAnalysis.aspx

Government Formulary List (GFL)

Document enumerating the non-proprietary names of medicinal products, vitamins, food supplements, and borderline substance available within the National Health Services; describes the dosage form and strength, disease category, prescriber criteria, Schedule V condition, and/or protocol number for medicinal entries[2]

Green Prescription

Special prescription required for dispensing controlled medicines with narcotic and/or psychotropic properties[3]

Medicine-specific Reasons

Operationally-defined as the medicinal item deemed as not approved during the medicines approval process

Occurrence

Operationally-defined as the degree to which the potential failure mode may happen as measured using a five-point ordinal scale based on Phase 1 results

[2] Government of Malta. The Government Formulary List [Internet]. Malta: Ministry of Health; 2020 [cited 2021 May 14]. Available from URL: https://deputyprimeminister.gov.mt/en/pharmaceutical/Pages/formulary/formulary.aspx

[3] Government of Malta. Pharmacy of Your Choice FAQs [Internet]. Malta: Ministry of Health; 2020 [cited 2021 May 14]. Available from URL: https://deputyprimeminister.gov.mt/en/poyc/Pages/360°-One-Stop-Shop-Service-Concept/Medicines-Approval/FAQ's.aspx

Pareto Analysis

Quality improvement technique to ensure concentration of interventions are carried out in the most efficient way; also known as 80/20 principle (Gorener and Toker, 2013)

Partial Non-approval

Operationally-defined as Schedule V applications in which only a part or a portion of the applied entitlements were not approved (e.g. omeprazole was not approved for an application submitted for both clopidogrel and omeprazole under the Ischaemic Heart Disease Schedule V condition)

Pharmacy of Your Choice (POYC) Scheme

A system in which the patient collects free pharmaceuticals from the local pharmacy of their choice, as deemed entitled through the Schedule V Scheme[4]

Potential Failure Modes

Refers to the errors or defects in the process; refers to the ways in which a process could not meet its specification criteria[5]

Process-specific Reasons

Operationally-defined as the reason relating to the steps in the medicines approval process which resulted to the non-approval of a medicinal item

[4] Government of Malta. POYC About Us [Internet]. Malta: Ministry of Health; 2020 [cited 2021 May 14]. https://deputyprimeminister.gov.mt/en/poyc/Pages/About%20Us.aspx

[5] American Society for Quality. Failure Mode and Effects Analysis [Internet]. ASQ; 2021 [cited 2021 May 14]. Available from URL: https://asq.org/quality-resources/fmea

Protocol

Guidelines on the restricted use of a medicinal product as approved within the National Health Services;[6] indicates the prescriber criteria, Schedule V condition, and duration approval for permit issued for protocol-regulated medicines

Schedule V Document

Document that contains information of the patient and their entitlement records to free medications, which can then be presented to their pharmacy of choice for collection of the required medication free of charge; also known as yellow paper or yellow card[7]

Schedule V Scheme

A medicine approval system in which patients are approved for entitlement to free pharmaceuticals based on the Social Security Act (Chapter 318) Article 23 and its amendment - Act No. I of 2012[8]

Sent-back Applications

Operationally-defined as Schedule V applications initially not processed and then returned back to either the patient or healthcare professional due to missing or wrong information preventing medicines approval officers from accessing patient or healthcare professional credentials

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[6] Government of Malta. Glossary[Internet]. Malta: Ministry of Health; 2020 [cited 2021 May 14]. Available from URL: https://deputyprimeminister.gov.mt/en/pharmaceutical/Pages/formulary/glossary.aspx

[7] Government of Malta. Pharmacy of Your Choice FAQs [Internet]. Malta: Ministry of Health; 2020 [cited 2021 May 14]. Available from URL: https://deputyprimeminister.gov.mt/en/poyc/Pages/360°-One-Stop-Shop-Service-Concept/Medicines-Approval/FAQ's.aspx

[8] Government of Malta. Chapter 318: Social Security Act [Internet]. Malta; 1987 [cited 2021 May 14]. Available from URL: https://deputyprimeminister.gov.mt/en/pharmaceutical/Documents/cap_318.pdf

Severity

Operationally-defined as the degree to which the potential failure mode may cause delay in treatment as measured using a five-point ordinal scale

Risk Priority Number

Numerical value assigned to a potential failure mode by calculating product of Severity, Occurrence, and Detectability[9]

[9] Institute for Healthcare Improvement. Risk Priority Number (from Failure Modes and Effects Analysis) [Internet]. IHI; 2021 [cited 2021 May 14]. Available from URL: http://www.ihi.org/resources/Pages/Measures/RiskPriorityNumberfromFailureModesandEffectsAnalysis.aspx

List of Abbreviations

ACEI	Angiotensin-converting Enzyme Inhibitor
CARE	Centralised Aid for Repository Entitlement
CCF	Corradino Correctional Facility
COE	Certificate of Entitlement
CPSU	Central Procurement and Supplies Unit
DPA	Directorate for Pharmaceutical Affairs
EMT	Exceptional Medicine Treatment
EU	European Union
FMEA	Failure Mode and Effects Analysis
GFL	Government Formulary List
GORD	Gastro-oesophageal Reflux Disease
HbA1c	Glycated haemoglobin or Haemoglobin A1c
LDL	Low-density Lipoprotein
MAS	Medicines Approval Section
MDH	Mater Dei Hospital
MMSE	Mini-mental State Examination
MTHFR	Methylenetetrahydrofolate reductase
NHS	National Health Service
NSTEMI	Non- ST segment Elevation Myocardial Infarction
OECD	Organisation for Economic Co-operation and Development
PCI	Percutaneous Coronary Intervention
POYC	Pharmacy Of Your Choice

PPC	Prescription Prepayment Certificate
RPN	Risk Priority Number
SLH	St. Luke's Hospital
SPC	Summary of Product Characteristics
STEMI	ST segment Elevation Myocardial Infarction
TAVI	Transcatheter Aortic Valve Replacement
UK	United Kingdom

Chapter 1

Introduction

1.1 Setting the scene: Pharmacy of Your Choice (POYC)

The Pharmacy of Your Choice (POYC), a unique national health service model initiated by the Ministry for Health, is responsible to ensure equitable accessibility to the Maltese Government's free pharmaceutical services in a timely, accurate, and efficient manner. Before the implementation of POYC in 2007, free pharmaceutical products were dispensed through government pharmacies in five health centres and hospitals across Malta and Gozo. Due to a limited number of dispensing points, patients used to travel farther from their homes and wait longer to be accommodated due to large number of patients converging from surrounding localities.[1]

In view of these concerns, a patient-centred approach has served as the core of the implementation of POYC operations necessary to achieve a balance between its operation and social objectives. Dispensing points were decentralised from government pharmacies to a private pharmacy of the patient's own choice to facilitate a more comfortable access to the government's free pharmaceutical services. As of 2021, POYC performed health-related functions including (a) approval of medicinal entitlements through the national free medicinal products scheme, (b) registration and renewal of dangerous drugs control card, (c) management of voucher scheme for patients with Coeliac disease, and (d) domiciliary delivery scheme for patients aged 70 years and older.[2]

[1] National Audit Office (NAO). Performance Audit: An Analysis of the Pharmacy of Your Choice Scheme. Malta: NAO; 2012.
[2] Government of Malta. Pharmacy of Your Choice About Us [Internet]. Malta: Ministry of Health; 2020 [cited 2021 May 14]. Available from URL: https://deputyprimeminister.gov.mt/en/poyc/Pages/About%20Us.aspx

1.1.1 Medicines approval system within POYC

In Malta, as per Social Security Act (Chapter 318) Article 23 and its amendment - Act No. I of 2012,[3] patients suffering from chronic conditions listed under the second part of Fifth Schedule of the Social Security Act (Appendix 1) are entitled to free medicinal treatments regardless of means, income, or age through the Schedule V Scheme. Patients can access these free medicinal entitlements from POYC upon approval according to the Schedule V scheme (Figure 1.1).

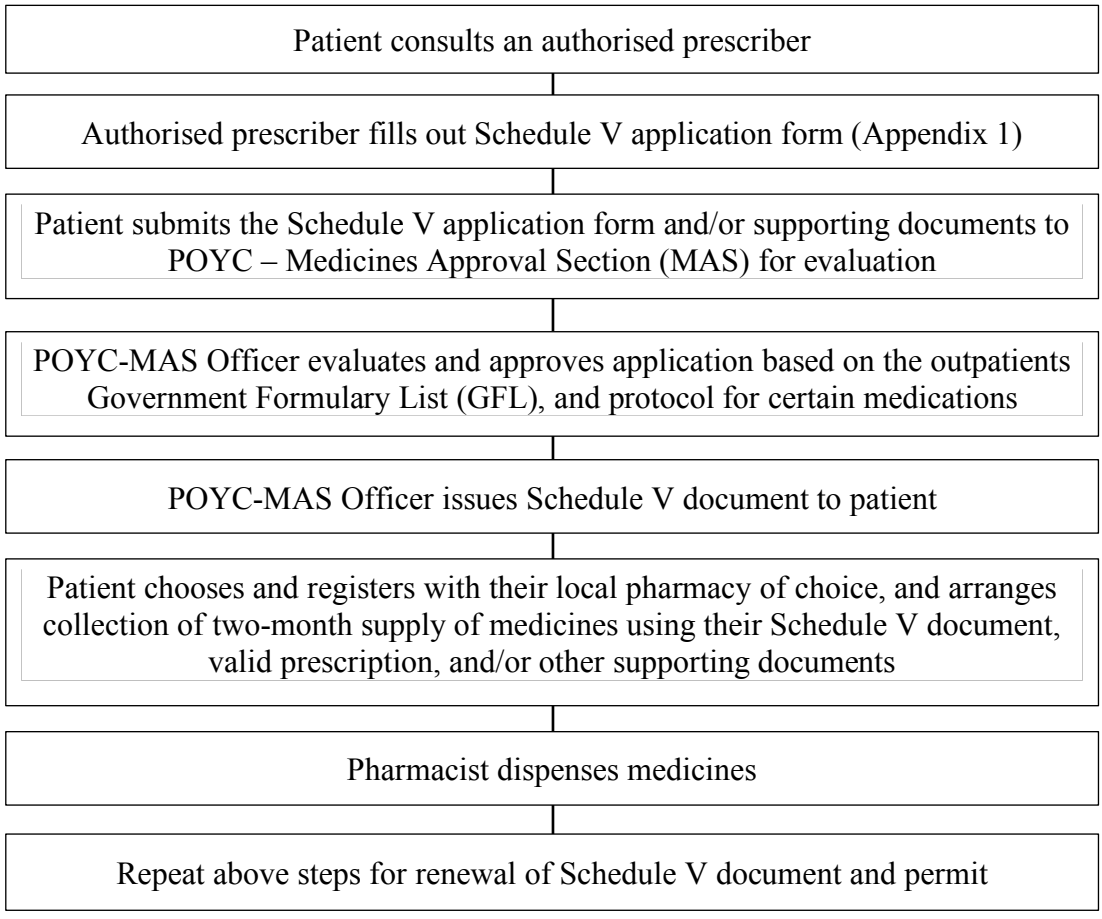

Figure 1.1. Steps in the POYC medicines approval system

[3] Government of Malta. Chapter 318: Social Security Act [Internet]. Malta; 1987 [cited 2021 May 14]. Available from URL: https://deputyprimeminister.gov.mt/en/pharmaceutical/Documents/cap_318.pdf

Evaluation and approval of applications for the Schedule V scheme, as carried out by POYC-MAS officers who are either pharmacists or pharmacy technicians, are based on factors such as drug/s requested, dosage form and regimen, duration of therapy, reason/s for the drug being requested, and availability of supporting documents as required by government protocols. Applications must contain accurate patient information, and duly signed by authorised prescribers within the specialisation stipulated on the GFL. Once an entitlement is approved, a Schedule V document is issued for 10 years for Maltese citizens for the majority of the chronic conditions (Appendix 1), except for Table 1.1:[4]

Table 1.1. Schedule V conditions with validity of less than 10 years

Schedule V Condition	Validity
A. Addiction Disorders	5 years
B. Endometriosis and Adenomyosis	6 months
C. Enzyme Disorders	Up to 6 weeks postpartum
D. Gestational Diabetes	Up to 6 weeks postpartum
E. Hepatitis B and C	1 year
F. Hospital Acquired Infections	6 months
G. Malignant Diseases	5 years
H. Precocious Puberty	5 years
I. Tuberculosis	1 year

[4] Office of the Deputy Prime Minister: Ministry for Health. DH Circular 742018: Re: Validity Period of Schedule V Cards [Internet]. Malta; 2018 [cited 2021 May 14]. Available from URL: https://deputyprimeminister.gov.mt/en/pharmaceutical/Documents/Circulars/2018/circular_74_2018.pdf

The pharmaceutical products in the scheme are determined by the Directorate for Pharmaceutical Affairs (DPA) through the implementation of European Union (EU) legislations in the area of formulary management, and through detailed research and consultations with stakeholders.[5] A specific form of the GFL, which is the Out Patient's Formulary List, has been made available particularly for government pharmacies and the Schedule V scheme. In this form, medicines were mapped to Schedule V conditions to which they can be approved as entitlements.[6] Certain medicines on the formulary are further regulated by protocols, which describe the prescriber criteria, indication of use, and duration of protocol-regulated permit approval.[7] Patients requiring treatments not in line with the government formulary list or protocols may apply for Exceptional Medicine Treatment (EMT) request (Appendix 1) through their prescribers. EMT applications are reviewed based on evidences on rationale for drug use, drug efficacy and safety, available treatment guidelines, cost of treatment, and cost comparison with alternative treatments.[8] The disposition regarding the EMT request is liaised by DPA with POYC for issuance of a Schedule V document.

[5] Government of Malta. Formulary Management Unit [Internet]. Malta: Ministry of Health; 2020 [cited 2021 May 14]. Available from URL: https://deputyprimeminister.gov.mt/en/pharmaceutical/Pages/formulary.aspx
[6] Government of Malta. The Government Formulary List [Internet]. Malta: Ministry of Health; 2020 [cited 2021 May 14]. Available from URL: https://deputyprimeminister.gov.mt/en/pharmaceutical/Pages/formulary/formulary.aspx
[7] Government of Malta. Protocols [Internet]. Malta: Ministry of Health; 2020 [cited 2021 May 14]. Available from URL: https://deputyprimeminister.gov.mt/en/pharmaceutical/Pages/formulary/Protocols.aspx
[8] Government of Malta. Exceptional Medicinal Treatment [Internet]. Malta: Ministry of Health; 2020 [cited 2021 May 14]. Available from URL: https://deputyprimeminister.gov.mt/en/pharmaceutical/Pages/EMT.aspx

In terms of dispensing points for the medicinal entitlements, patients are required to be registered with the pharmacy of their choice participating in the scheme, except for medicinal items labelled as "TBDF (to be dispensed from) Hospital" as per the GFL. The following documents must be validated by the pharmacist prior to dispensing: (a) patient's ID card, (b) a valid prescription by a medical practitioner, and the (c) Schedule V document with relevant permits. Additional documents, such as the green prescription and control card, are required for controlled drugs that are considered as narcotic and/or psychotropic. Patients are dispensed a supply sufficient for 56 days at a time, or 28 days for controlled drugs, and are instructed to return before their current stock is finished, together with the same requirements listed above.[9]

The principal stakeholders in the Schedule V scheme would include POYC, CPSU, DPA, participating pharmacies, and end-clients/patients.[10] Figure 1.2 shows the delineated functions of the stakeholders in the distribution of pharmaceuticals.

[9] Government of Malta. Pharmacy of Your Choice FAQs [Internet]. Malta: Ministry of Health; 2020 [cited 2021 May 14]. Available from URL: https://deputyprimeminister.gov.mt/en/poyc/Pages/360°-One-Stop-Shop-Service-Concept/Medicines-Approval/FAQ's.aspx

[10] National Audit Office (NAO). Performance Audit: An Analysis of the Pharmacy of Your Choice Scheme. Malta: NAO; 2012.

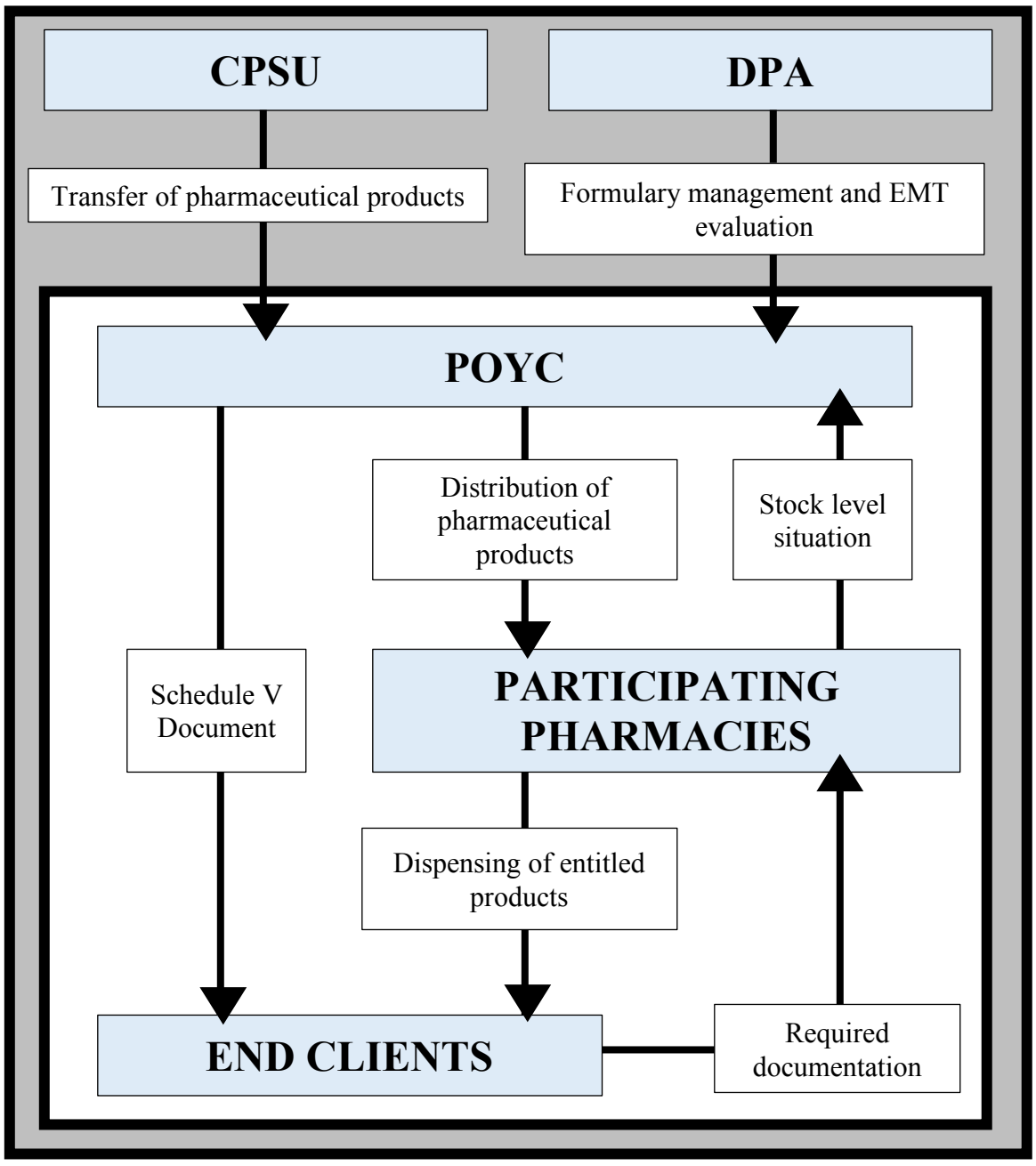

Figure 1.2. Schematic diagram of stakeholder functions in the Schedule V scheme

1.1.2 Non-approval of Schedule V applications

As of August 2019, an estimated total of 147,000 patients, corresponding to one-third of the population in Malta,[11] have been enrolled to the scheme, with 222 participating private community pharmacies[12] as dispensing points for free medicinal treatments across Malta and Gozo.

In the Ministry for Health Annual Report for 2013, there were a recorded 50,251 and 21,168 applications received and processed for the Schedule V Scheme and protocol-regulated items, respectively.[13] The Ministry for Health noted that 3184 requests in 2013 for protocol-regulated items were not approved due to failure to follow set protocols and policies as per the GFL.[14] Such non-approvals could mean that the patient would either have to buy the medicine privately from a pharmacy, or decide to delay their treatment by not taking the medicine in cases of financial incapacity or inability to communicate back with their prescriber to discuss alternatives. These delays in receiving treatment may pose health risks to patients that could be dependent on the severity of the condition and on the point at which

[11] Television Malta. 147,000 patients use Pharmacy of Your Choice Scheme[Internet]. Malta; 2019 [cited 2021 May 14]. Available from URL: https://www.tvm.com.mt/en/news/147000-patients-use-pharmacy-of-your-choice-scheme/

[12] Government of Malta. List of Community Pharmacies Providing POYC services in Malta and Gozo. Malta; Pharmacy of Your Choice; 2020 [cited 2021 May 14]. Available from URL: https://deputyprimeminister.gov.mt/en/poyc/Documents/New%20content%20VA/Website%20list.pdf

[13] Ministry for Health. Annual Report 2013 [Internet]. Malta: Ministry for Health; 2013 [cited 2021 May 14]. Available from URL: https://www.gov.mt/en/Government/Government%20of%20Malta/Ministries%20and%20Entities/Annual%20Government%20Reports/Documents/Annual%20Reports%202013/Ministry%20for%20Health%20Annual%20Report%202013.pdf

[14] Ministry for Health. Annual Report 2013 [Internet]. Malta: Ministry for Health; 2013 [cited 2021 May 14]. Available from URL: https://www.gov.mt/en/Government/Government%20of%20Malta/Ministries%20and%20Entities/Annual%20Government%20Reports/Documents/Annual%20Reports%202013/Ministry%20for%20Health%20Annual%20Report%202013.pdf

patients could have access to the same treatment through out-of-pocket expenses, or to an alternative treatment if available.

1.1.3 Health spending in Malta and comparison between POYC and other government-funded chronic disease treatment schemes

Malta has experienced one of the highest increases in total health expenditure per capita in the EU from 2007 to 2017 at 60% to reach € 2732.[15] In comparison to health services in other countries, Malta provides practically universal coverage through the Schedule V and POYC schemes by shouldering the full cost of pharmaceuticals in which patients are deemed entitled for, as evaluated based on a set of approval criteria.[16] Despite this, Malta was still the fourth highest in the EU in 2017 in terms of out-of-pocket expenditures amounting to 34.6% of the total health expenditure, with pharmaceutical spending attributing to 8.5%. Health expenditure is expected to further increase in the coming years as a result of an ageing and growing Maltese population, and optimising cost-effectiveness and efficiency of the health system is necessary to augment future growth in health spending.[17]

[15] Organisation for Economic Cooperation and Development/European Observatory on Health Systems and Policies. State of Health in the EU: Malta Country Health Profile 2019 [Internet]. OECD; 2019 [cited 2021 May 14]. Available from: https://www.euro.who.int/__data/assets/pdf_file/0005/419468/Country-Health-Profile-2019-Malta.pdf

[16] Organisation for Economic Cooperation and Development. Addressing Challenges in Access to Oncology Medicines Analytical Report [Internet]. OECD; 2020 [cited 2021 May 14]. Available from URL: https://www.oecd.org/health/health-systems/Addressing-Challenges-in-Access-to-Oncology-Medicines-Analytical-Report.pdf

[17] Organisation for Economic Cooperation and Development/European Observatory on Health Systems and Policies. State of Health in the EU: Malta Country Health Profile 2019 [Internet]. OECD; 2019 [cited 2021 May 14]. Available from: https://www.euro.who.int/__data/assets/pdf_file/0005/419468/Country-Health-Profile-2019-Malta.pdf

In Australia, the Pharmaceutical Benefits Scheme allows the residents to have access to a list of medicines at a government-subsidised price, with patient co-payments (Mellish et al., 2015) and with better subsidies offered to concessional status, including pensioners, low-income earners, and indigenous people with or at risk for chronic conditions.[18] Canada's universal health insurance system covers physician visits, hospitalisations, and diagnostic tests regardless of income and demographic status (Martin et al., 2018), while coverage for prescription drugs still remain as a mixture between public and private insurance funding dependent on patient eligibility, co-payments, and formulary listing (Daw and Morgan, 2012). The Medicines Reimbursement System in Netherlands allows for full or partial reimbursements for medicines by private social health insurers.[19] The Dutch system emphasises patient choice in terms of selecting between health insurers based on the flexibility of providers contracted and the insurer's level of service, thereby creating a managed field for competition among private insurers in offering the best value-for-money ratio for the citizens (Victoor et al., 2012). Insurance premiums are being kept low through preferential policy, in which most health insurers only cover the cheapest version of a medicine.[20]

In the United Kingdom (UK), the National Health Service (NHS) is the government-funded medical service for UK residents. The NHS in England requires certain people to pay a portion of the prescription costs, while such costs in Wales, Scotland, and Northern Ireland

[18] Department of Human Services. Closing the Gap—PBS co-payment measure [Internet]. Canberra; 2015 [cited 2021 May 14]. Available from URL: http://www.humanservices.gov.au/health-professionals/services/pbs-closing-the-gap-co-payment-measure/.
[19] Government of the Netherlands. Keeping medicines affordable. Netherlands [cited 2021 May 14]. Available from URL: https://www.government.nl/topics/medicines/keeping-medicines-affordable
[20] Government of the Netherlands. Keeping medicines affordable. Netherlands [cited 2021 May 14]. Available from URL: https://www.government.nl/topics/medicines/keeping-medicines-affordable

are budgeted for by the government.[21] As of April 2021, each prescription item in England would cost £ 9.35. Patients categorised as elderly aged 60 years and older, children, 16 to 18 year-olds in full-time education, pregnant women or have had given birth in the previous 12 months, or person with continuing physical disability are entitled for free prescriptions. Similar with the Schedule V conditions in Malta, NHS prescriptions for various conditions including cancer, epilepsy, permanent fistula, hypoadrenalism, diabetes insipidus or other forms of hypopituitarism, hypoparathyroidism, myasthenia gravis, and myxedema, are considered free through a medical exemption certificate.[22] A unique feature of the NHS is the choice to avail a prescription prepayment certificate (PPC) for patients who foresee use of numerous prescription items at a certain time. For example, a three-month PPC could be availed for £ 30.25 to cover all NHS prescriptions. A patient not eligible for free prescriptions, and is needing six prescriptions items would have to pay £ 56.10, while a patient on a three-month PPC would only need to pay for £ 30.25 provided that the items are to be prescribed during the validity period of the PPC.

1.2 Delay in access to care and its impact

Treatment delay is defined as the time lag from diagnosis of a disease to the first initiation of treatment (Bello et al., 2019). According to Reichert and Jacobs (2018), delays in accessing treatment through a publicly funded health care system may decrease the utility gain of a patient from the treatment itself. In an economic point of view, such delays may

[21] Full Fact. What is the NHS? [cited 2021 May 14]. Available from URL: https://fullfact.org/health/what-is-the-nhs/

[22] National Health Service. Who can get free prescriptions? [cited 2021 May 14]. Available from URL: https://www.nhs.uk/nhs-services/prescriptions-and-pharmacies/who-can-get-free-prescriptions/

result in the treatment having a lesser value when consumed in the future relative to its current value, and with patients incurring additional intangible costs due to pain, anxiety, disability, and uncertainty. While majority of the medicines may be bought through out-of-pocket expenses, patients would opt to prioritise and spend for food, housing, and other basic necessities over medical treatments (Richard et al., 2018). These delays could further be considered as inefficiencies as the government providing the service does not generate any benefits from it (Heinrich et al., 2018).

In a setting where treatment delays may be encountered, the populations identified to be most vulnerable were those with chronic illnesses, the financially-challenged, and the elderly (DiMatteo, 2004; Prentice and Pizer, 2007). Weissman et al (1991) added that patients who were uninsured or without regular physician had 40% to 80% greater odds of reporting delays in care. A cross-sectional observational study by Reisinger and colleagues (2018) among adult patients in the United States of America using the data from the Centers for Disease Control Behavioral Risk Factor Surveillance System pointed out that patients lacking social support were twice likely to delay needed medical care as compared to patients with social support, with such association still present even after adjusting for socio-economic status, presence of comorbidities, and access to care. Perceptual, social, and behavioral factors were suggested by Mandelzweig and others (2006) to play a role in the multi-dimensional nature of treatment delays. These factors would include the patient's perception of symptom severity and control, their appreciation of the meaning of their symptoms, and the advice they receive from social circles as to when to seek care. Cultural and religious beliefs, such as seeking help from traditional healers to manage conditions, were further cited by Mhalu and colleagues (2019) to be associated with treatment delays.

Delays in accessing innovative and orphan drugs were found to be of concern in the EU. Potential root causes identified to be causing unavailability and delays to these types of drugs were the speed of regulatory process and the financial readiness of the health system to support decision and infrastructure.[23] In a recent analysis made by OECD (2020) on the availability of 109 oncology product/indication pairs across five types of cancers, Malta had the lowest percentage of product/indication pairs with approved marketing authorisation at 46%, with Denmark and Germany as the highest at 91% and 88%, respectively.[24] In the context of POYC, treatment delays may stem from structural variables such as formulary and protocol restrictions narrowing the eligibility of patients who could receive free entitlements, and the complexities of procedures and policies governing the scheme.

Studies, particularly in the areas of oncology, cardiology, and psychiatry, have been published to illustrate how delays in accessing treatment may impact patient lives. According to Chen et al. (2011), patients who have not received treatment on time were significantly less probable to identify themselves as having excellent or very good ex post health status, in addition to having significantly less quality-of-life scores as compared to a group who never had experienced delays.

[23] European Federation of Pharmaceutical Industries and Associations. The root cause of unavailability and delay to innovative medicines: Reducing the time before patients have access to innovative medicines [Internet]. EU; 2020 [cited 2021 May 14]. Available from URL: https://www.efpia.eu/media/554527/root-causes-unvailability-delay-cra-final-300620.pdf

[24] Organisation for Economic Cooperation and Development. Addressing Challenges in Access to Oncology Medicines Analytical Report [Internet]. OECD; 2020 [cited 2021 May 14]. Available from URL: https://www.oecd.org/health/health-systems/Addressing-Challenges-in-Access-to-Oncology-Medicines-Analytical-Report.pdf

Mortality and morbidity were shown to be of primary concerns among patients experiencing delays in care. In a national population-based modelling study conducted by Maringe and colleagues (2020) in the United Kingdom during the COVID-19 pandemic, it was found that diagnostic delays needed to jumpstart cancer treatment for breast, colorectal, oesophageal, and lung cancers are expected to significantly increase the number of avoidable deaths due to cancers. The same results were consistently reported in a systematic review and meta-analysis conducted by Hanna and others (2020) involving 34 studies. A significant association was found between increase in mortality rates and cancer treatment delay, of even up to four weeks, across patients receiving surgical, systemic, or radiotherapy interventions for seven types of cancer. For time from referral to treatment, a median of four weeks was observed among those with breast cancer, eight weeks for colorectal cancer, lung cancer, and lymphoma, and 15 weeks for prostate cancer (Comber et al., 2005).

In patients with heart problems, particularly those with ST-segment elevation myocardial infarction (STEMI) acute coronary syndrome, higher mortality was recorded among women, aged 75 years and older, with diabetes, and requesting medical care from home who delayed seeking medical care the longest (Rivero et al., 2016). When treatment is delayed among patients with acute coronary syndrome, larger infarct size and higher probability of disability may result as a consequence, as stated by Moser and colleagues (2006). Reasons for such delays cited in a cross-sectional study-design by Taghaddosi et al. (2010) involving patients with STEMI were that patients believed that the problem or symptoms would resolve on its own, or that the symptoms could be disregarded or attributed to other problems not involving the heart.

Response to future treatment may also be impacted by treatment delays as seen in the study by Drake and colleagues (2020). Their longitudinal and modelling study predicted that patients with longer duration of untreated psychosis would have reduced treatment response, underlining the importance for quick access to a range of treatments, particularly in the starting weeks of the onset of psychosis. A systematic review and meta-analysis of 33 studies further reported that more severe positive and negative symptoms and poor social functioning could be attributed to delayed access in treatment for patients with untreated psychosis (Pentilla et al., 2014). The median delays in treatment among patients with other psychiatric conditions such as anxiety disorders, mood disorders, and substance use disorders were found to be from 3 to 30 years, 1 to 14 years, and 6 to 18 years, respectively (Wang et al., 2007).

Apart from health and humanistic outcomes, cost-related outcome was measured by Kraft et al. (2009) in a study involving the effect of delays in seeking care to wasting and C-reactive proteins among children younger than 5 years. On average, it was identified that hospitalisation costs were 1.9% higher among those who had delays in treatment. Several patient-related factors such as family income, education, and health insurance coverage were reported to contribute to the disparities with respect to access to timely delivery of health service. According to an analysis made by Haque (2020) in the United States, a one-day delay in medical treatments may incur an additional total hospital cost of 14.1%, and further delaying it to six days, may increase the additional cost to around 95%.

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1.3 Management of risks associated with delay in care

Root causes of delays in treatment could be considered by health systems for proper analysis and management. In a health service model such as POYC, management of risks is necessary and warranted to pro-actively and systematically increase the quality of service rendered to patients, while at the same time, decreasing financial and operational costs (Park and Sharp, 2019) and increasing brand value and community standing.[25] The workloads of employees could also be reduced when systems are in place to reduce risks (Huang et al., 2018). Risk management covers activities from detection, monitoring, assessing, mitigating, and preventing risks.[21] Tools that may be used in healthcare to analyse risks may include cause-consequence analysis, checklists, event tree analysis, failure modes and effects analysis (FMEA), fault tree analysis, and hazard and operability analysis. [26]

The roles of pharmacists in curbing issues related to delays in treatment have been documented. In a review by Holt and Hand (1999), pharmacists were reported to develop an intervention where patients diagnosed with coronary heart disease were counselled regarding the need for early detection of symptoms of acute myocardial infarction, and the advantages that come with prompt assessment and treatment. In a pharmacist-physician collaborative management in a multiple myeloma clinic, it was found that oncology pharmacists performing medication reviews and medicines access-related problem solving have resulted

[25] NEJM Catalyst. What is Risk Management in Healthcare? [Internet]. Massachusetts; 2018 [cited 2021 May 14]. Available from URL: https://catalyst.nejm.org/doi/full/10.1056/CAT.18.0197
[26] Glancey J. Failure Analysis Methods: What, Why, and How [Internet]. University of Delaware; 2006 [cited 2021 May 14]. Available from URL: http://research.me.udel.edu/~jglancey/FailureAnalysis.pdf

in a significant 85% reduction in the number of delays in obtaining immunomodulatory drugs from fifteen days to seven (Sweiss et al., 2018).

1.4 Rationale of the study

The Joint Commission's Office of Quality and Safety in 2015 showed that delays in treatment have been found to stem from inadequate assessments, poor planning, communication failures, and human factors.[27] Safety actions recommended by The Joint Commission involved improvement of health information technology and access to care. While DPA and POYC–MAS have implemented safety actions through revision of protocols and the GFL[28] to reduce bottlenecks arising from bureaucratic processes and to ensure that treatment is more readily available, it is recommended that further risk management is performed in order to optimise service delivery.

There is limited data and documentation published regarding delays that could be attributed primarily to the medicines approval system in the context of POYC. Available information could be found from The Ministry for Health Annual Report for 2013 which discussed the statistics of non-approvals in POYC–MAS and compared the number of

[27] The Joint Commission. Preventing delays in treatment. Quick Safety (Issue Nine) [Internet]. Division of Health Care Improvement [cited 2021 May 14]. Available from URL: https://www.jointcommission.org/-/media/deprecated-unorganized/imported-assets/tjc/system-folders/joint-commission-online/quick_safety_issue_nine_jan_2015_finalpdf.pdf?db=web&hash=D5C49298D4FCB08F66F710FDFFD8CFC3

[28] Government of Malta. List of Changes [Internet]. Malta: Ministry of Health; 2020 [cited 2021 May14]. Available from URL: https://deputyprimeminister.gov.mt/en/pharmaceutical/Documents/GFL/list_of_changes_gfl_Jan_2021.pdf

requests for approval of protocol-regulated items processed in 2012 and 2013.[29] The succeeding annual reports from the Ministry of Health, however, did no longer presented approval and non-approval data for the Schedule V scheme. The performance audit conducted by the National Audit Office (2012) has only covered the stock movement and quality of dispensing service based on end-client feedback and participating pharmacy perspectives.[30] In the study by Fenech and Azzopardi (2013) regarding POYC, pharmacist intervention was assessed only at the point of contact in the community pharmacy level. Proposals on implementation of medication review and electronic prescribing within the POYC scheme to improve relationship between the pharmacists and patients were tackled by Bonnici (2015).[31]

In terms of studies regarding delays in treatment, researches mostly covered emergency department settings (Guzman, et al., 2019), pathway to surgery (Pande et al. 2019), and diagnostic errors in malignancies (Kompelli et al., 2019) and tuberculosis (Bojovic et al., 2018), but not those arising from the time at which medicinal entitlements are vetted for approval in a national health service model.

[29] Ministry for Health. Annual Report 2013 [Internet]. Malta: Ministry for Health; 2013 [cited 2021 May 14]. Available from URL: https://www.gov.mt/en/Government/Government%20of%20Malta/Ministries%20and%20Entities/Annual%20Government%20Reports/Documents/Annual%20Reports%202013/Ministry%20for%20Health%20Annual%20Report%202013.pdf

[30] National Audit Office (NAO). Performance Audit: An Analysis of the Pharmacy of Your Choice Scheme. Malta: NAO; 2012.

[31] University of Malta. Dissertation Abstracts and Project Descriptions 2015 – Pharmacy of Your Choice – Where Are We Going? Patient and Pharmacist Forum (Hannah Bonnici) [Internet]. Malta: Department of Pharmacy, Faculty of Medicine and Surgery; 2015 [cited 2021 May 14]. Available from URL: https://www.um.edu.mt/library/oar/bitstream/123456789/48762/1/Dissertation_abstracts_and_project_descriptions_2015.pdf

In view of the scarcity of data in the area of medicines approval system, there is a need to generate current evidence as to how POYC can better adhere to its mandate of ensuring equitable accessibility to free pharmaceutical services.

1.5 Aim and Objectives

The aim of this research was to optimise the POYC medicines approval system through pharmacist interventions to promote an efficient service delivery to patients. The primary objectives of the study were to:

A. Characterise the reasons for non-approval of Schedule V applications
B. Evaluate the risks associated with non-approval of Schedule V applications, and
C. Develop pharmacist interventions targeted to streamline access to approval of Schedule V applications

The secondary objective of the study was to assess the status of non-approvals during the COVID-19 pandemic.

Chapter 2

Methodology

2.1 Research overview

The research was divided into three phases to achieve the aims and objectives. The main steps in the research were summarised in a schematic diagram in Figure 2.1.

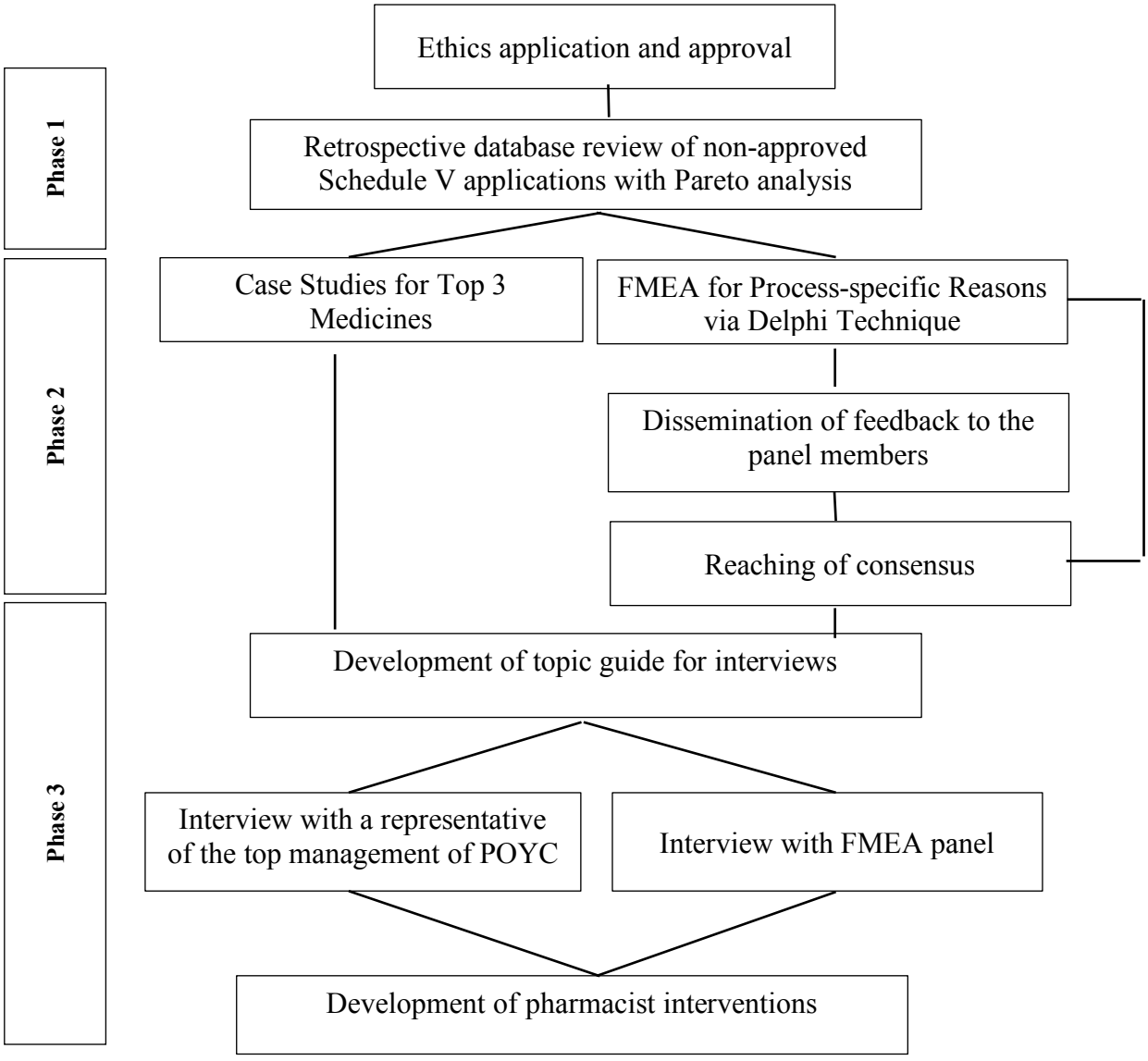

Figure 2.1. Schematic diagram for the key steps in the research

2.2 Research setting and design

The research was conducted at POYC–MAS of St. Luke's Hospital (SLH), Mater Dei Hospital (MDH), and Floriana Health Centre. The research utilised a mixed-method three-phased development design as summarised in Table 2.1. Quantitative data was collected in the analysis of the reasons of non-approvals and in the evaluation of risks associated with it, while qualitative information was derived from different POYC stakeholders to develop pharmacists interventions targeted to streamline access to approval of Schedule V applications.

Table 2.1. Methodology design

Phase	Research Objectives	Type of Data	Data Collection
Phase 1	To characterise the reasons for non-approval of Schedule V applications	Quantitative	Retrospective Database Review and Pareto Analysis
Phase 2	To evaluate the risks associated with non-approval of Schedule V applications	Quantitative	FMEA via Delphi Technique
Phase 3	To develop pharmacist interventions targeted to streamline access to approval of Schedule V applications	Qualitative	Key Informant Interviews

2.3 Research data management plan and statistical analysis

A data management plan was prepared to identify the following for each of the research objectives: (a) information and variables needed for the study, (b) data collection method and instrument, (c) source of data, (d) analysis of data, and (e) data coding and access.

Microsoft® Excel for Mac (version 16.16.12) was used for data presentation and analysis using descriptive statistics. IBM SPSS Statistics for Macintosh, Build 1.0.0.1508 64-bit edition was used for statistical tests including independent samples t-test and Pearson's correlation.

2.4 Ethics application and approval

The permission to conduct research at POYC-MAS was requested, and granted by the Chief Executive Officer of POYC. Permission for unpublished secondary data and institutional approval for access to data were granted by the POYC Data Controller and Data Protection Officer. Ethics approval was received from the Faculty of Medicine and Surgery Research Ethics Committee (Appendix 2).

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2.5 Phase 1: Characterisation of reasons for non-approval of Schedule V applications

Schedule V non-approvals were categorised with the corresponding operational definitions by the researcher:

A. **Partial Non-approval** - Schedule V applications in which only a part or a portion of the applied entitlements were not approved (for example, omeprazole was not approved for an application submitted for both clopidogrel and omeprazole under the Ischaemic Heart Disease Schedule V condition)

B. **Full Non-approval** - Schedule V applications in which all items in the application form were not approved (for example, both clopidogrel and omeprazole were not approved for an application submitted for both clopidogrel and omeprazole under the Ischaemic Heart Disease Schedule V condition)

C. **Foreign Patients Application** - Schedule V applications of foreign patients initially not processed due to unavailability of supporting documents to prove eligibility for the Schedule V scheme

D. **Sent-back Applications** – Schedule V applications initially not processed and then returned back to either the patient or healthcare professional due to missing or wrong information preventing medicines approval officers from accessing patient or healthcare professional credentials

2.5.1 Retrospective database review of non-approvals

Schedule V non-approvals saved in the POYC-MAS Microsoft® Excel databases meeting the following criteria were included as samples for retrospective analysis:

A. Application was evaluated between January 2012 and October 2020
B. Application had complete non-approval information
    a. Identity of non-approved entitlement for partial non-approvals
    b. Reason for non-approval
    c. Date

For partial non-approvals, both the frequency counts for medicine-specific and process-specific reasons for non-approvals were determined for each year from 2012 to 2020. Only the frequency count of process-specific reasons was determined for each year for full non-approvals as the database only considered what were the process-specific reasons for not approving the application, regardless of which medicines are being applied for. The frequency counts of process-specific reasons for both partial and full non-approvals were added to identify their occurrence for the Phase 2 of the study. Frequency counts for each year for sent-back and foreign patients applications were identified. The yearly frequency counts for each non-approval category were plotted in a line graph, and then analysed for trends.

2.5.2 Pareto analysis of reasons for non-approvals

A Pareto analysis was performed for partial and full non-approvals by calculating the percentages of medicine-specific and process-specific reasons then ranked from highest to lowest. The lists of medicine-specific and process-specific reasons contributing to 80% of the cases of partial or full non-approvals were generated. Due to a large number of medicine-specific reasons (n=102) cumulatively contributing to 80% of partial non-approvals, only the items with the ten highest percentages were considered for priority reasons.

2.5.3 Status of non-approvals during the COVID-19 pandemic

The status of non-approvals during the COVID-19 pandemic was identified by using a six-month summary of COVID-19 cases in Malta from March 2020, when the first case was reported, until August 2020. The monthly summary of the frequency counts of medicine- and process-specific reasons for partial and full non-approvals, sent-back, and foreign patients applications for the same time period was sought.

An overlapping time-plot was generated to compare the monthly frequency of non-approvals from March 2020 to August 2020 during the pandemic, against the monthly frequency of non-approvals from the same months in the previous year (March 2019 to August 2019). One-tailed t-test between two independent sample means was performed to determine if there was a statistically significant difference between the cases of non-approvals before and during the pandemic, with a level of significance of 0.05. The null hypothesis for the test states that there is no difference in the mean non-approval cases before

and during the pandemic. The alternative hypothesis states that the mean non-approval cases before the pandemic is less than the mean non-approval cases during the pandemic.

The relationship between the monthly total new and active COVID-19 cases and the monthly frequency counts of non-approvals was investigated using Pearson's correlation analysis with a level of significance of 0.05. A positive correlation efficient would indicate a direct relationship, while a negative correlation coefficient would indicate an inverse relationship.

2.6 Phase 2: Evaluation of risks associated with non-approval of Schedule V applications

The risks associated with non-approval of Schedule V applications were evaluated using two methods: (a) case study analysis for the top three medicine-specific reasons, and (b) FMEA for all process-specific reasons identified from the Phase 1 of the research.

2.6.1 Development of case studies on top medicine-specific reasons for non-approvals

Based on the Pareto analysis, the top medicine- and process-specific reasons for non-approvals contributing to a cumulative 80% of the cases were generated. The top three medicine-specific reasons for non-approvals (clopidogrel, levothyroxine, and omeprazole) identified from the Phase 1 of the study were selected for case studies. Clopidogrel, levothyroxine, and omeprazole were described based on their pharmacologic properties and

GFL specifications, particularly the formulary dosage form and strength, prescriber criteria, Schedule V conditions they can be approved under, and protocol regulation, as applicable. The clinical indications were described based on the Summary of Product Characteristics (SPC) published by the manufacturer. The total number of patients with valid Schedule V documents for the three medicines as of March 2021 were also included, based on the records of POYC. The process-specific reasons for non-approval of clopidogrel, levothyroxine, and omeprazole were characterised using two time points: before the pandemic (January 2012 to October 2020), and during the pandemic (March 2020 to August 2020). Pareto analysis was conducted using the two time points to identify the process-specific reasons responsible for 80% of the non-approval cases of each particular medicine.

One tailed t-tests between two sample means were performed for each of the top three medicine-specific reasons to determine if there were statistically significant differences between the cases of non-approvals before and during the pandemic, with a level of significance of 0.05. Relationships between the monthly COVID-19 cases and the monthly frequency counts of non-approvals for each of the top three medicine-specific reasons were investigated using Pearson's correlation analysis, with a level of significance of 0.05.

Further analysis was made by identifying direct costs associated with the treatment and describing the risks when such treatment is delayed based on published literature. The maximum annual total cost for entitlement of clopidogrel, levothyroxine, and omeprazole were computed by identifying the unit cost based of government tender, then multiplying it with the number of units required for the maximum dose based on the SPC, then by 365 days, and then by the total number of patients entitled with the treatment.

2.6.2 FMEA of process-specific reasons for non-approvals via Delphi Technique

FMEA was performed to systematically evaluate the potential failure modes in the POYC medicines approval system using a Delphi panel composed of two POYC pharmacists, one community pharmacist employed in a participating pharmacy in the POYC scheme, and one resident specialist in respiratory medicine with rights to apply for entitlements in the Schedule V scheme. The panel was selected based on expertise, experience, and involvement in the Schedule V scheme. The researcher served as the facilitator responsible for summarising the responses of the panelists and for providing feedback to the panel.

This part was divided into three stages: (a) Idea Generation Stage, (b) Delphi Round 1, and (c) Delphi Round 2. In the idea generation stage, the panelists were asked to identify the potential failure modes of the POYC medicines approval system using the process-specific reasons for non-approvals from Phase 1, to operationally define variables and grading scales for Severity, Occurrence, and Detectability, and to construct a 2x2 risk matrix stratifying the levels of risks involved in the system. Case descriptions were also identified by the panelists for each of the potential failure modes to provide contextual meaning.

After the contents of the FMEA tool were finalised in the Idea Generation Stage, the Delphi rounds ensued to allow the panel to grade the Severity, Occurrence, and Detectability of each potential failure modes. In between the two rounds of Delphi, the facilitator computed for the mean values of Severity, Occurrence, and Detectability for each potential failure modes. The FMEA tool was updated with the mean values, and was then forwarded to each

of the panelists to re-grade their response with the primary objective of converging into a consensus.

The endpoint for the Delphi was preliminarily set to finish after two rounds, in which the rounded-off values of the mean responses for Severity, Occurrence, and Detectability were used as the final scores in the FMEA. The RPN was calculated using the product of Severity, Occurrence, and Detectability for ranking, with a maximum score of 125. The RPNs for all the potential failure modes were summed up to calculate the Total Process RPN for the POYC medicines approval system.

The results of the FMEA were then shared with the panel to ensure agreement on the final scores for the Severity, Occurrence, Detectability, and RPNs for each of the potential failure modes. The whole FMEA procedure followed the timeline as shown in Table 2.2.

The Severity, Occurrence, and Detectability for each of the potential failure modes were plotted in a risk matrix to stratify risks whether they are critical, high, moderate, or minor. Higher bearing on the Severity, as compared to Occurrence and Detectability, was considered in the preparation of the risk matrix. Potential failure modes stratified as critical risks were considered as priorities in the Phase 3 of the research.

Table 2.2. Timeline and tasks for the FMEA via Delphi technique

Day and Round	Facilitator and Panelists Tasks
1 (Idea Generation)	Facilitator provided the copy of the FMEA template, grading scales, and risk matrix Panelists provided feedback regarding the FMEA template, grading scales, and risk matrix
3	Panelists submitted feedback regarding the FMEA template, grading scales, and risk matrix Facilitator collated and summarised responses
4 (Round 1)	Facilitator provided final FMEA template, grading scales, and risk matrix Panelists graded the severity, occurrence, and detectability of potential failure modes
7	Panelists submitted feedback Facilitator collated and summarised mean responses
8 (Round 2)	Facilitator provided FMEA template with feedback from Round 1 Panelists graded the severity, occurrence, and detectability of potential failure modes
10	Panelists submitted feedback Facilitator collated and summarised mean responses
11	Facilitator shared the final FMEA output with the panelists

2.7 Phase 3: Development of pharmacist interventions targeted to streamline access to approval of Schedule V applications

Since the FMEA Delphi panel was composed of stakeholders primarily involved in the POYC medicines approval system, it was deemed necessary by the researcher to also involve them in the development of pharmacist interventions. Preliminary interventions were suggested by the panelists for each of the potential failure modes. Common intervention themes were determined and then mapped for each of the potential failure modes.

An interview guide was developed based on the results of Phase 2 and from the preliminary interventions suggested by the FMEA Delphi panel. A personal meeting and interview with the Responsible Person of POYC was held to discuss key points listed in the interview guide. Key points for discussion were about the (a) feasibility and probability of adapting the suggested interventions for the implementation of the optimisation of the POYC medicines approval system, (b) other additional interventions that were not yet raised in Phase 2, (c) key personnel responsible for carrying out interventions, and (d) outcome measures that can be used to determine success of the interventions to be implemented (Appendix 3).

Chapter 3

Results

3.1. Reasons for non-approval of Schedule V applications

A total of 36,108 non-approvals were recorded between January 2012 and October 2020 based from the non-approval databases kept by POYC-MAS. These were further categorised into the following: 74% partial non-approvals, 12% foreign patient applications, 10% full non-approvals, and 4% sent-back applications. Table 3.1 summarised the yearly distribution of the types of non-approvals.

Table 3.1. Summary of non-approvals per year between 2012 and 2020 (N=36108)

Year	Partial	Full	Sent-back	Foreign Patients
2012	5612	499	67	797
2013	5577	540	187	728
2014	4774	272	148	340
2015	3073	150	51	283
2016	2462	184	109	460
2017	1573	220	28	360
2018	1143	214	55	290
2019	981	650	49	281
2020	1590	981	604	776
Total	**26785**	**3710**	**1298**	**4315**

For partial non-approvals, both the medicine- and process-specific reasons were identified. It was found that there were 661 unique medicines not approved during the studied period. There were a total of 21 process-specific reasons for partial non-approvals, and the top 10 with their corresponding occurrences were: medicine did not correspond to Schedule V condition (43%), no MAS permit application (16%), application not according to government protocol (10%), medicine not on the formulary (7%), awaiting exceptional approval from DPA (6%), no supporting document as required by government protocol (3%), wrong prescriber criteria (2%), patient must renounce other government entitlements (1%), must specify medicine (0.4%), and prescriber used the wrong form (0.3%). Figure 3.1 shows a decreasing trend in the frequency count of partial non-approvals, except for an increase in 2020.

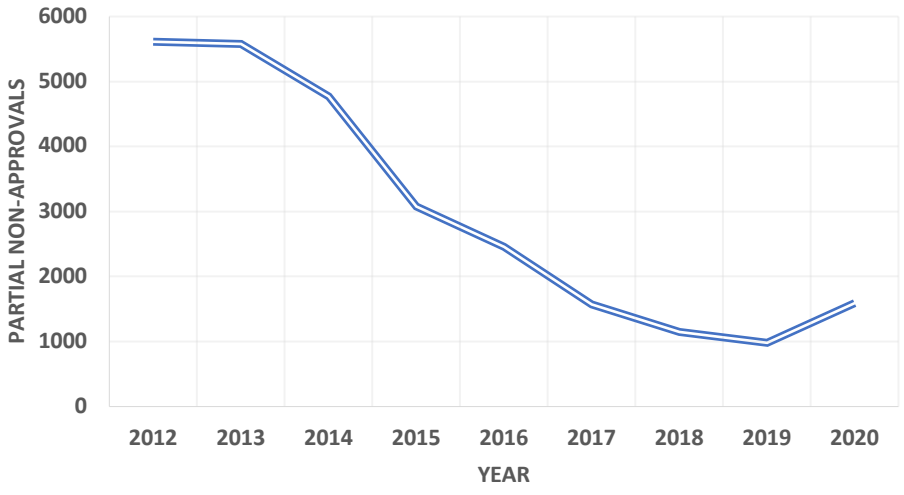


Figure 3.1. Trend in partial non-approvals between 2012 and 2020

A total of 21 process-specific reasons for full non-approvals were identified, and the top 10 with their corresponding occurrences were: medicine did not correspond to Schedule V condition (22%), application not according to government protocol (15%), no MAS permit application (11%), no supporting document as required by government protocol (10%), prescriber did not apply for Schedule V (7%), prescriber not eligible to apply for Schedule V (6%), patient failed to bring the original Schedule V application (4%), medicine not on the formulary (4%), prescriber did not sign the Schedule V application form (4%), and patient must renounce other government entitlements (3%). In contrast with partial non-approvals, the frequency count for full non-approvals has been increasing gradually since 2018 onwards (Figure 3.2).

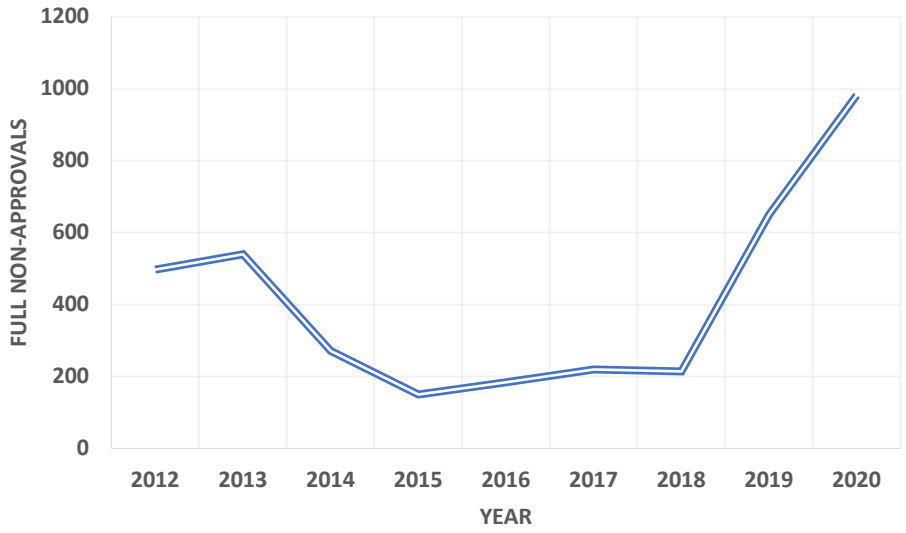


Figure 3.2. Trend in full non-approvals between 2012 and 2020

Foreign patient applications also showed the same trend as full non-approvals wherein cases have decreased from 2012, but has increased by 275% from 2019 (Figure 3.3.) Sent-back applications showed the steepest increase from 2019 at 1200%, from a trend with relatively consistently low cases since 2012 (Figure 3.4).

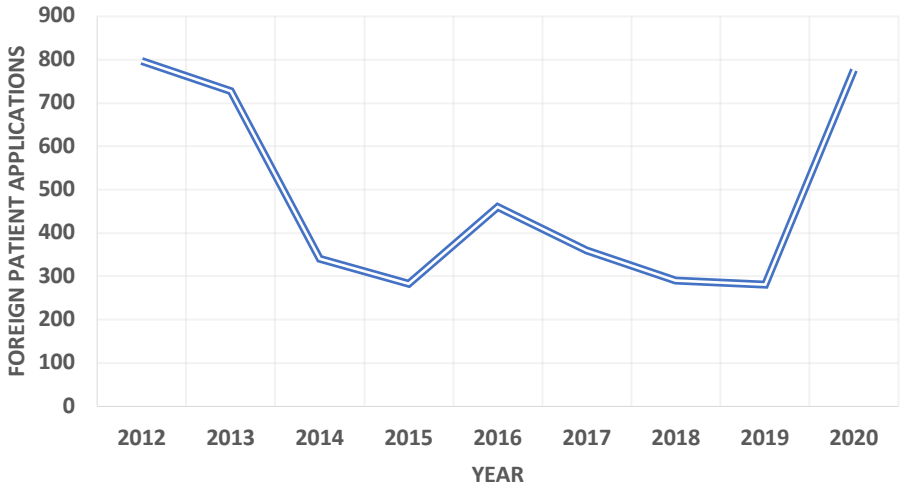


Figure 3.3. Trend in foreign patient applications between 2012 and 2020

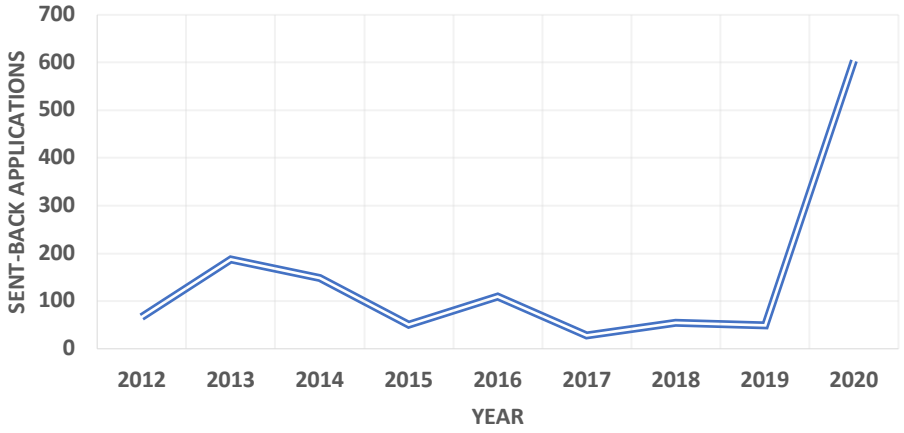


Figure 3.4. Trend in sent-back applications between 2012 and 2020

3.2 Pareto analysis of reasons for non-approval of Schedule V applications

Pareto Principle or the 80/20 Rule was utilised to identify the top medicine-specific reasons contributing to the 80% of the cases of partial non-approvals. The analysis showed that 15% (102 out of the 661 unique medicine-specific reasons) contributed to 80% of partial non-approvals. The top 10 medicine-specific reasons with their corresponding occurrence were: clopidogrel (8%), levothyroxine (5%), omeprazole (4%), vitamins (unspecified, 3%), atorvastatin (3%), valsartan/candesartan (3%), folic acid (2%), lactulose (2%), oral iron (2%), and ipratropium (2%).

In terms of process-specific reasons, 80% of the cases for partial non-approvals could be attributed to 5 out of the 21 recorded process-specific reasons, while there were 8 out of 21 for full non-approvals. In both types of non-approvals, medicines not corresponding to the Schedule V condition were the top process-specific reason corresponding to half of the cases of partial non-approvals, and a quarter for full non-approvals. Other common process-specific reasons between partial and full non-approvals were that the application was not according to government protocol, there were no MAS permit application, or the medicine was not available on GFL. A ranking and comparison between the results of Pareto analysis for partial and full non-approvals are summarised in Table 3.2.

Table 3.2. Process-specific reasons for partial and full non-approvals based on Pareto Analysis

Ranking	Process-specific Reasons	
	Partial Non-approval	**Full Non-approvals**
1	Medicine did not correspond to Schedule V condition	Medicine did not correspond to Schedule V condition
2	No MAS permit application	Application not according to government protocol
3	Application not according to government protocol	No MAS permit application
4	Medicine not on the formulary	No supporting document as required by government protocol
5	Awaiting exceptional approval from DPA	Prescriber did not apply for Schedule V
6	N/A	Prescriber not eligible to apply for Schedule V
7	N/A	Patient failed to bring the original Schedule V application
8	N/A	Medicine not on the formulary

3.3 Impact of the COVID-19 pandemic on the POYC medicines approval system

Based on the COVID-19 data published by the World Health Organization[32] and Malta Ministry for Health[33] online, total new COVID-19 cases, total new recoveries, end of month active cases, end of month total cases, end of month total deaths, and end of month total recoveries were identified (Table 3.3). Total new cases, total new recoveries, and end of month active cases have shown a decrease from April to June 2020, and an increase again until August 2020. In response to the COVID-19 cases, modifications in the medicines approval system were implemented to ensure safety (Table 3.4)

Table 3.3. Monthly COVID-19 statistics in Malta between March and August 2020

Month (2020)	Total New Cases	Total New Recoveries	End of Month			
			Active Cases	Total Cases	Total Deaths	Total Recoveries
March	156	0	156	156	0	0
April	306	348	110	462	4	348
May	155	186	75	617	9	534
June	53	106	21	670	9	640
July	154	25	150	824	9	665
August	1059	735	471	1883	12	1400
Total	**3058**	**2562**	**N/A**	**N/A**	**N/A**	**N/A**

[32] World Health Organization. Malta Situation [Internet]. WHO; 2020 [cited 2021 May 14]. Available from URL: https://covid19.who.int/region/euro/country/mt

[33] Ministry for Health. Sahha [Internet]. Malta; 2020 [cited 2021 May 14]. Available from URL: https://www.facebook.com/sahhagovmt

Table 3.4. Comparison between the original and modified POYC medicines approval system in view of the COVID-19 pandemic

Original Procedure	Modified COVID-19 Procedure
A. Patient consults an authorised prescriber	Patient consults an authorised prescriber
B. Authorised prescriber fills out Schedule V application form	Authorised prescriber fills out Schedule V application form
C. Patient submits the Schedule V application form and/or supporting documents to POYC-MAS for evaluation	Patient leaves the Schedule V application form and/or supporting documents in a mailbox at POYC-MAS for evaluation, or the authorized prescriber submits electronically
D. POYC-MAS Officer evaluates and approves application based on the outpatients GFL and protocol for certain medications	POYC-MAS Officer evaluates and approves application based on the outpatients GFL and protocol for certain medications
E. POYC-MAS Officer issues Schedule V document to patient	POYC-MAS Officer sends Schedule V document and notification regarding non-approval by post
F. Patient goes to their local pharmacy of choice with their Schedule V document and valid prescription from any doctor and/or other supporting documents to arrange collection of two-month supply of medicines	Patient goes to their local pharmacy of choice with valid prescription from any doctor and/or other supporting documents to arrange collection of two-month supply of medicines
G. Pharmacist dispenses medicines	Pharmacist dispenses medicines
H. Repeat Steps A to G for renewal of Schedule V document and permit	Repeat Steps A to G for renewal of Schedule V document and permit

A total of 2,857 non-approvals were recorded during the six-month period from March until August 2020 according to the non-approval databases kept by POYC-MAS. These were further categorised into: 40% partial non-approvals, 24% full non-approvals, 20% foreign patient applications, and 16% sent-back applications. As compared to the data before the pandemic, the same ranking can be observed except that full non-approvals and foreign patient applications have changed their ranking positions. Table 3.5 summarises the monthly distribution of non-approvals during the COVID-19 pandemic.

Table 3.5. Summary of non-approvals during a six-month period during the COVID-19 pandemic (N=2857)

Month (2020)	Partial	Full	Sent-back	Foreign Patients
March	120	66	15	49
April	120	59	46	68
May	203	114	79	103
June	248	153	116	123
July	220	136	119	116
August	220	147	96	121
Total	**1131**	**675**	**471**	**580**

An overlapping time-plot (Figure 3.5) showed that monthly non-approvals during the COVID-19 pandemic were consistently higher as compared to the same six-month period before the pandemic. Both situations showed an increase in non-approvals for the month of June, which then gradually decreased until the month of August.

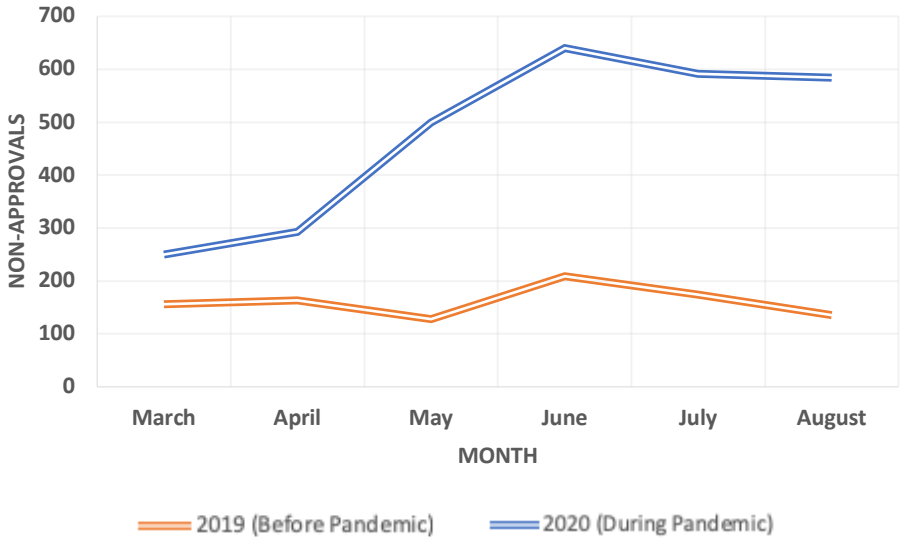


Figure 3.5. Trend in non-approvals during a six-month period pre- and during COVID-19 pandemic

Period considered were March to August 2019 and March to August 2020

Two independent sample means of non-approvals before and during the pandemic were statistically analysed using one-tailed t-test. Equality of variances were not assumed since the F-test significance ($p = 0.003$) is less than the level of significance, 0.05. It can be concluded that the mean non-approvals before the pandemic was significantly lower as compared to during the pandemic ($t=4.597$, $p=0.0025$).

To analyse the relationship between the monthly total new and active COVID-19 cases and the monthly frequency counts of non-approvals, Pearson's correlation analysis with a level of significance of 0.05 was performed. It was found that there was no sufficient evidence to conclude that there was a significant correlation between the monthly total new ($p= 0.747$) and active COVID-19 cases ($p=0.798$), and the monthly frequency counts of non-approvals.

3.4 Case Study 1: Clopidogrel

As of March 2021, there were 1925 Schedule V documents and permits which have been issued for clopidogrel, and with all under Ischaemic Heart Disease. As per GFL specifications,[34] clopidogrel is available as 75mg tablets, and can be applied for by a Consultant Physician only for the Schedule V condition Ischaemic Heart Disease.

Clopidogrel is a protocol-regulated item as per Protocol 276.[35] The protocol must be satisfied for a patient to be issued a permit for clopidogrel. The protocol has two parts wherein Part A states that it can be applied for by a Consultant Physician only for the Schedule V condition Ischaemic Heart Disease when a patient has either undergone a percutaneous coronary intervention (stent report should be attached with the application) or has been admitted to hospital with acute coronary syndrome (hospital admission dates should be

[34] Directorate for Pharmaceutical Affairs. Out-Patients Formulary List January 2021[Internet]. Malta: Ministry for Health; 2021 [cited 2021 May 14]. Available from URL: https://deputyprimeminister.gov.mt/en/pharmaceutical/Documents/GFL/out_patients_gfl_jan_2021.pdf

[35] Directorate for Pharmaceutical Affairs. 276 Clopidogrel 75mg Tablets [Internet]. Malta: Ministry for Health; 2021 [cited 2021 May 14]. Available from URL: https://deputyprimeminister.gov.mt/en/pharmaceutical/Documents/Protocols/276.pdf

specified on application), for a permit duration of up to 12 months starting from date of percutaneous coronary intervention (PCI) or hospital admission. Requests for renewal of permit shall not be accepted as clopidogrel has a maximum duration of approval of one year only. Patients who were switched over from ticlopidine to clopidogrel as per DH Circular No. 174/2011[36] shall be exempted from the clause pertaining to renewals. Part B states that clopidogrel can be applied for by either a Consultant Cardiologist or Consultant Cardiac Surgeon only for the Schedule V condition "Ischaemic Heart Disease" when a patient has undergone transcatheter aortic valve implantation (TAVI) (TAVI report should be attached with the application), for a permit duration of up to six months starting from date of TAVI.

Based on the SPC, clopidogrel is indicated for the (a) secondary prevention of atherothrombotic events and (b) prevention of atherothrombotic and thromboembolic events in atrial fibrillation. In terms of secondary prevention of atherothrombotic events, it can be used among adults suffering from myocardial infarction, ischaemic stroke, or established peripheral arterial disease. It is also indicated in patients suffering from acute coronary syndromes, such as non-ST segment myocardial infarction (NSTEMI) and ST segment myocardial infarction (STEMI), in combination with aspirin.[37]

[36] Government of Malta. DH Circular No. 174/2011: Re: Deletion of Ticlopidine & changeover to clopidogrel [Internet]. Malta: Ministry for Health, The Elderly and Community Care; 2011 [cited 2021 May 14]. Available from URL: https://deputyprimeminister.gov.mt/en/pharmaceutical/Documents/Circulars/2011/circular_174_2011.pdf

[37] Aurobindo Pharma -Milpharm Ltd. Clopidogrel 75mg film-coated tablets SmPC [Internet]. Middesex; 2021 [cited 2021 May 14]. Available from: https://www.medicines.org.uk/emc/product/5207/smpc

Between January 2012 and October 2020, a total of 2202 non-approvals were recorded for clopidogrel. There were 15 process-specific reasons responsible for its non-approval, with the three reasons attributing to more than 80% of its non-approval cases as per Pareto analysis: no MAS permit application (35%), application not according to government protocol (34%), and no supporting document as required by government protocol (25%). Figure 3.6 shows a decreasing trend in the frequency count of clopidogrel non-approvals until 2019, then an increase in 2020.

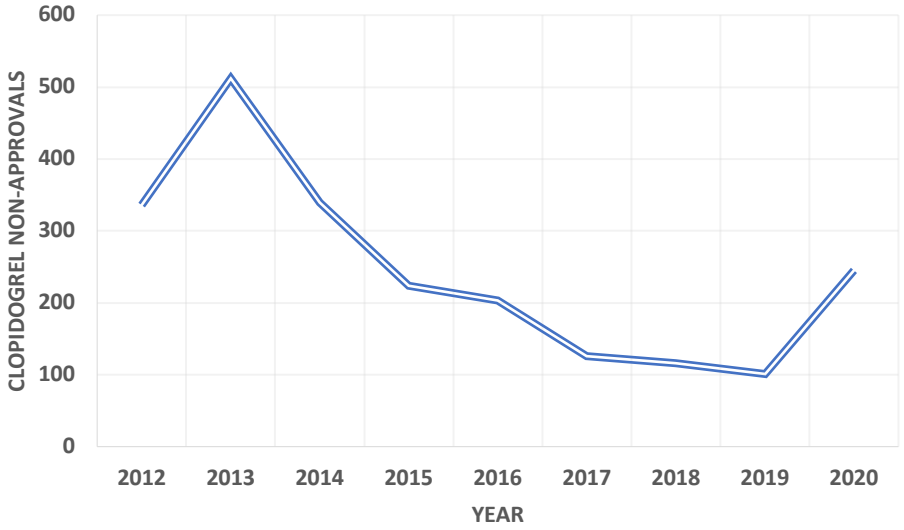


Figure 3.6. Trend in clopidogrel non-approvals between 2012 and 2020

In a six-month period during the COVID-19 pandemic (March 2020 to August 2020), clopidogrel was the top medicine-specific reason for non-approval, responsible for 17% of the partial non-approval cases (n=1131). By Pareto analysis, two out of seven process-specific reasons were recorded to attribute to more than 80% of clopidogrel non-approvals:

no supporting document as required by government protocol (75%), and no MAS permit application (16%).

Two independent sample means of non-approvals of clopidogrel before and during the pandemic were statistically analysed using one-tailed t-test. Equality of variances were not assumed since the F-test significance ($p = 0.001$) is less than the level of significance, 0.05. It can be concluded that the mean non-approvals for clopidogrel before the pandemic was significantly lower as compared to during the pandemic ($t=20.467$, $p=0.0025$).

To analyse the relationship between the monthly total new and active COVID-19 cases and the monthly frequency counts of clopidogrel non-approvals during the pandemic, Pearson's correlation analysis with a level of significance of 0.05 was performed. It was found that there was no sufficient evidence to conclude that there was a significant correlation between the monthly total new ($p= 0.180$) and active COVID-19 cases ($p=0.095$), and the monthly frequency counts of clopidogrel non-approvals.

Based on an awarded contract regarding a government call for quotation for the provision of clopidogrel 75mg tablets (102,000 units), the winning bid amounted to a total of € 6,000.[38] The estimated value for each clopidogrel 75mg tablet was € 0.02. In relation to the posology, adults clinically-indicated to take clopidogrel are usually recommended a

[38] Etenders,gov.mt. Call for Quotes for the Provision of Clopidogrel 75mg Tablets [Internet]. Malta; 2015 [cited 2021 May 14]. Available from URL: https://www.etenders.gov.mt/epps/cft/prepareViewCfTWS.do?resourceId=1747100

single daily dose of 75mg.[39] Patients with NSTEMI should be initiated with 300mg loading dose of clopidogrel, then continued with 75mg daily in combination with 75 to 300mg of aspirin for up to 12 months based on clinical trial data. Patients with STEMI are initiated with 300mg loading dose of clopidogrel in combination with aspirin, with or without thrombolytics, continued for at least four weeks, then 75mg of clopidogrel alone daily. This would mean that on average, the government will be paying a maximum of € 7.30 for every adult patient needing clopidogrel annually, or € 14,052 for the 1,925 patients entitled under the Schedule V condition Ischaemic Heart Disease.

The protocol for clopidogrel requires that a patient attach a PCI or TAVI report, or a case summary indicating hospital admission due to acute coronary syndromes. Patients being discharged from MDH are given with a three-day supply of clopidogrel to give time for the Schedule V application and approval. In cases wherein there is delay in the approval of Schedule V, data suggests that the premature discontinuation of clopidogrel is associated with increased risk of secondary myocardial infarction, death, or higher health-related costs (Kubica et al., 2016; Luu et al., 2019). It has also been shown that there is a relatively low rate of continuing clopidogrel among patients discharged from hospital (Luu et al., 2019). Unnecessary use of Clopidogrel is usually associated with bleeding, but rarely fatal (Mauri et al., 2016; Elmariah et al., 2018).

[39] Aurobindo Pharma -Milpharm Ltd. Clopidogrel 75mg film-coated tablets SmPC [Internet]. Middesex; 2021 [cited 2021 May 14]. Available from: https://www.medicines.org.uk/emc/product/5207/smpc

In a study conducted by Soekhlal and colleagues (2013) on the treatment costs associated with myocardial infarction in Netherlands, it was estimated that the mean treatment costs were at € 5,021, with PCI contributing largely in the increase in cost, and the length of stay and type of hospital as the strongest predictors. This could mean that three failed attempts to prevent a secondary atherothrombotic events, specifically myocardial infarction, would already offset the annual cost for providing clopidogrel to 1,925 entitled patients. In terms of risk associated with inappropriate use of clopidogrel, the mean initial in-hospital costs for patients admitted with acute upper gastrointestinal bleeding in the UK was reported by Campbell and others (2015) to be at £ 2,458 (€ 2,854), with inpatient bed days, blood transfusion, and endoscopy as the key cost drivers. The nationwide population-based cohort study by Grove et al (2013) in Denmark has showed a modest risk of gastrointestinal adverse events associated with clopidogrel use, with an odds ratio of < 2.0.

3.5 Case Study 2: Levothyroxine

As of March 2021, there were 3124 Schedule V documents which have been issued for levothyroxine, with the majority issued under Malignant Diseases, Hypopituitarism, and Chronic Mood Disorders. As per GFL specifications,[40] levothyroxine is available as 50mcg or 100mcg tablets, and can be applied for by a Consultant for the following Schedule V conditions: (a) Malignant Diseases (n=1127), (b) Hypopituitarism (n=1019), (c) Chronic Mood Disorder (n=942), (d) Down Syndrome (n=36), and (e) Turner Syndrome (n=0).

[40] Directorate for Pharmaceutical Affairs. Out-Patients Formulary List January 2021[Internet]. Malta: Ministry for Health; 2021 [cited 2021 May 14]. Available from URL: https://deputyprimeminister.gov.mt/en/pharmaceutical/Documents/GFL/out_patients_gfl_jan_2021.pdf

Based on the SPC, levothyroxine is indicated for hypothyroidism control, congenital hypothyroidism in infants, acquired hypothyroidism in children, and juvenile myxedema.[41]

Between January 2012 and October 2020, a total of 547 non-approvals were recorded for levothyroxine. There were 10 process-specific reasons responsible for its non-approval, with only one attributing to more than 80% of its non-approval cases as per Pareto analysis: medicine did not correspond to Schedule V condition (86%). Figure 3.7 shows a consistently decreasing trend in the frequency count of levothyroxine non-approvals until 2020.

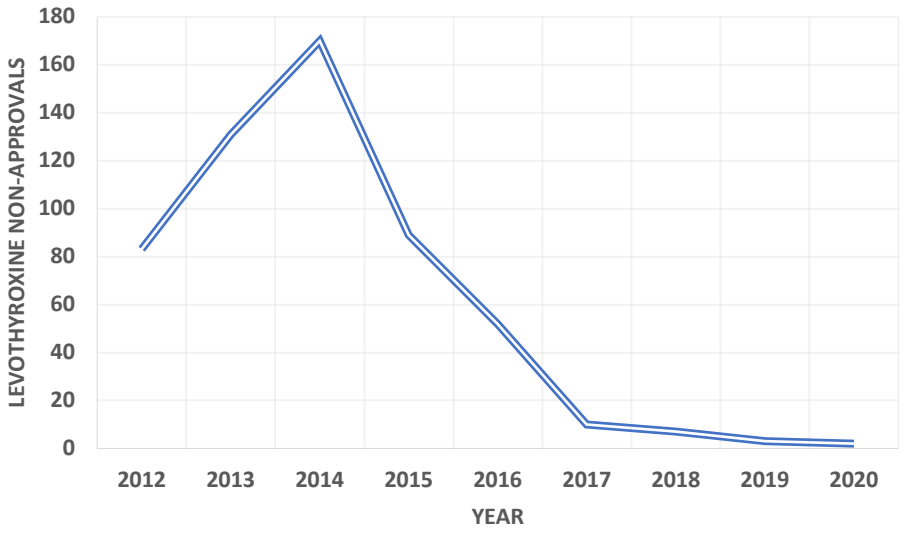


Figure 3.7. Trend in levothyroxine non-approvals between 2012 and 2020

[41] ADVANZ Pharma. Levothyroxine 100mcg tablets SmPC [Internet]. London; 2020 [cited 2021 May 14]. Available from URL: https://www.medicines.org.uk/emc/product/5682/smpc#PHARMACOLOGICAL_PROPS

In a six-month period during the COVID-19 pandemic (March 2020 to August 2020), levothyroxine has only one recorded non-approval case, in which the process-specific reason was that the medicine did not correspond to the Schedule V condition.

Two independent sample means of non-approvals of levothyroxine before and during the pandemic were statistically analysed using one-tailed t-test. Equality of variances were not assumed since the F-test significance ($p = 0.031$) is less than the level of significance, 0.05. It can be concluded that there was no sufficient evidence to say that the mean non-approvals for levothyroxine before the pandemic was significantly lower as compared to during the pandemic ($t=-0.500$, $p=0.319$).

Pearson's correlation analysis was not performed to analyse the relationship between the monthly total new and active COVID-19 cases and the monthly frequency counts of levothyroxine non-approvals during the pandemic, as only one month in a six-month period during the pandemic period has recorded a non-approval.

Based on the published call for tender for the supply of levothyroxine sodium 25mcg tablets (8,000,000 units) and 100mcg tablets (2,500,000 units), the estimated procurement value based on market research was € 432,500.[42] The estimated value for each 100mcg of levothyroxine was € 0.11. In relation to the posology, adults clinically-indicated to take levothyroxine are usually recommended an initial dose of 50 to 100mcg daily, and adjusted

[42] Etenders,gov.mt. Tender for the supply of levothyroxine sodium tablets/capsules [Internet]. Malta; 2019 [cited 2021 May 14]. Available from URL: https://www.etenders.gov.mt/epps/cft/listContractDocuments.do?resourceId=6941012

at three- to four-week intervals by 50mcg until normal metabolism is steadily maintained, with the final dose of up to 100 to 200mcg daily.[43] This would mean that on average, the government will be paying a maximum of € 80.30 for every adult patient needing levothyroxine annually, or € 250,857 for the population entitled under the Schedule V, assuming that the 3124 Schedule V documents for the five GFL Schedule V conditions are considered mutually-exclusive of each other.

A case report by Kandukuri and colleagues (2010) showed that non-adherence to levothyroxine when clinically-indicated may cause irreversible behavioral and cognitive changes in severe cases of hypothyroidism. However, unnecessary use of levothyroxine, especially among patients with only a borderline underactive thyroid, may result with risks such as irregular heartbeat, insomnia, and loss of bone density, without receiving any beneficial effect from it.[44]

3.6 Case Study 3: Omeprazole

As of March 2021, there were 32249 Schedule V documents which have been issued for omeprazole, and the majority were issued under Gastro-Oesophageal Reflux Disease (GORD), Gastric/Duodenal Ulcer, and Malignant Disease. As per GFL specifications,[45]

[43] ADVANZ Pharma. Levothyroxine 100mcg tablets SmPC [Internet]. London; 2020 [cited 2021 May 14]. Available from URL: https://www.medicines.org.uk/emc/product/5682/smpc#PHARMACOLOGICAL_PROPS

[44] Godman H. For borderline underactive thyroid, drug therapy isn't always necessary [Internet]. Harvard Health Publishing; 2019 [cited 2021 May 14]. Available from URL: https://www.health.harvard.edu/blog/for-borderline-underactive-thyroid-drug-therapy-isnt-always-necessary-201310096740

[45] Directorate for Pharmaceutical Affairs. Out-Patients Formulary List January 2021[Internet]. Malta: Ministry for Health; 2021 [cited 2021 May 14]. Available from URL: https://deputyprimeminister.gov.mt/en/pharmaceutical/Documents/GFL/out_patients_gfl_jan_2021.pdf

omeprazole is available as 20mg capsules, and can be applied for by a Consultant for the following 13 Schedule V conditions: (a) Gastro-Oesophageal Reflux Disease (n=23186), (b) Gastric/Duodenal Ulcers (n=4595), (c) Malignant Diseases (n=2211), (d) Crystal Deposition Disease (n=701), (e) Rheumatoid Arthritis (n=494), (f) Chronic Liver Disease (n=303), (g) Polymyalgia Rheumatica (n=225), (h) Lupus Erythematosus (n=151), (i) Spinal Cord Pathologies (n=122), (j) Spondyloarthritis (n=104), (k) Paget's Disease (n=87), (l) Polyarthritis Nodosa (n=37), and (m) Systemic Sclerosis (n=33)

Based on the SPC, omeprazole is indicated in adults for the treatment of gastric and duodenal ulcers, including the prevention of its relapse, reflux oesophagitis, symptomatic gastro-oesophageal reflux disease, and Zollinger-Ellison syndrome. For children over 1 year of age weighing at least 10kg, it is indicated for the treatment of reflux oesophagitis and symptomatic treatment of heartburn and acid regurgitation in gastro-oesophageal reflux disease.[46]

Between January 2012 and October 2020, a total of 1018 non-approvals were recorded for omeprazole. There were 14 process-specific reasons responsible for its non-approval, with only one attributing to more than 80% of its non-approval cases as per Pareto analysis: medicine did not correspond to Schedule V condition (87%). Figure 3.8 shows a consistent decline in the frequency count of omeprazole non-approvals since 2012, with a slight increase from 2019.

[46] Sandoz Limited. Omeprazole 20mg Capsules SmPC[Internet]. United Kingdom; 2020 [cited 2021 May 14]. Available from URL: https://www.medicines.org.uk/emc/product/4895/smpc#gref

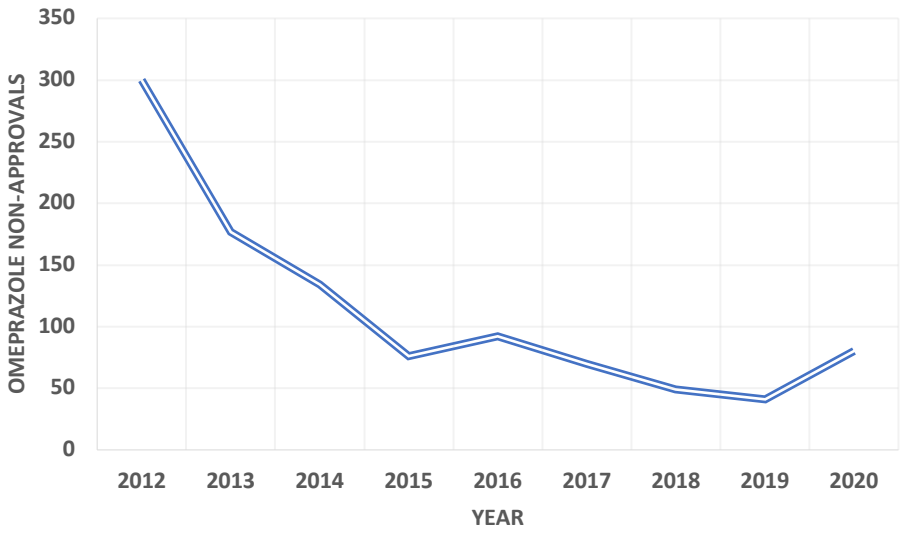


Figure 3.8. Trend in omeprazole non-approvals between 2012 and 2020

In a six-month period during the COVID-19 pandemic (March 2020 to August 2020), omeprazole had 80 non-approval cases, equivalent to 7% of the partial non-approval cases (n=1131). By Pareto analysis, only one out of seven process-specific reasons were recorded to attribute to more than 80% of omeprazole non-approvals: medicine did not correspond to Schedule V condition (86%), which was the same process-specific reason responsible for 87% of omeprazole non-approval cases before the COVID-19 pandemic.

Two independent sample means of non-approvals of omeprazole before and during the pandemic were statistically analysed using one-tailed t-test. Equality of variances were not assumed since the F-test significance ($p = 0.006$) is less than the level of significance, 0.05. It can be concluded that the mean non-approvals for omeprazole before the pandemic was significantly lower as compared to during the pandemic ($t=5.251$, $p=0.0015$).

To analyse the relationship between the monthly total new and active COVID-19 cases and the monthly frequency counts of omeprazole non-approvals during the pandemic, Pearson's correlation analysis with a level of significance of 0.05 was performed. It was found that there was no sufficient evidence to conclude that there was a significant correlation between the monthly total new (p= 0.085) and active COVID-19 cases (p=0.134), and the monthly frequency counts of omeprazole non-approvals.

Based on the published call for tender for the supply of omeprazole 20mg tablets (60,831,086 units), the estimated procurement value based on market research is pegged at € 1,034,128.[47] The estimated value for each 20mg of omeprazole was € 0.02. In relation to the posology, adults clinically-indicated to take omeprazole are usually recommended an initial dose of 20mg daily for four weeks, which can be extended for a further two to four weeks for treatment of ulcers. When used for long-term management, that is for GORD maintenance or prevention of relapse of drug-related ulcers, the recommended dose is 10mg once daily, which can then be increased to 20 to 40mg once daily.[48] This would mean that on average, the government will be paying a maximum of € 14.60 for every adult patient needing omeprazole annually, or € 470,835 for the population entitled under the Schedule V, assuming that the 32249 Schedule V documents for the 13 GFL Schedule V conditions are considered mutually-exclusive of each other.

[47] Etenders,gov.mt. Tender for the supply of omeprazole 20mg tablets/capsules [Internet]. Malta; 2020 [cited 2021 May 14]. Available from URL: https://www.etenders.gov.mt/epps/cft/listContractDocuments.do?resourceId=7185374

[48] Sandoz Limited. Omeprazole 20mg Capsules SmPC[Internet]. United Kingdom; 2020 [cited 2021 May 14]. Available from URL: https://www.medicines.org.uk/emc/product/4895/smpc#gref

Proton pump inhibitors like omeprazole are preferred for long-term management as compared to H_2 receptor antagonists, as the latter produces tolerance following repeated administration in two weeks, causing a gradual weakening of acid-suppressing activity (Kinoshita et al., 2018). The recurrence of GORD with continuous administration of proton pump inhibitors for one year were found to be less than 15%, as compared to those not receiving maintenance at a rate of greater than 50% (Pace et al., 2005). While there are benefits in using omeprazole, adverse effects from unnecessary use have also been recorded, including diarrhea (Shimura et al., 2012), acute interstitial nephritis (Berney-Meyer et al., 2014), and increased risks of cerebral and cardiac ischaemic attacks (Wang, 2017; Xie, 2017).

A cost analysis for GORD and peptic ulcer disease was conducted by Mahmood and McNamara (2003) across different countries in Europe. The overall cost for these disorders were estimated to be at € 253 per person, with 61% attributed to direct costs including physician visits, in-patient care with or without surgery, and investigations. When omeprazole is used inappropriately, a short-term increase in risk of pneumonia infections may be observed, with adjusted odds ratio of 3.21 (Sarkar et al., 2008). An increase in hospitalisation costs amounting to $ 15,682 (€ 12,863) may result from such serious adverse effect (O'Neill et al., 2013).

Given the information on the risks and benefits of using omeprazole for long-term maintenance therapy, healthcare professionals are recommended to re-confirm the necessity of prescribing it to patients, and ensuring that the benefits would outweigh the risks (Kinoshita et al., 2018).

3.7 FMEA of process-specific reasons for non-approvals via Delphi Technique

The Delphi panel has identified 25 potential failure modes in the POYC medicines approval system during the idea generation stage using the process-specific reasons for non-approvals characterised in Phase 1 (Appendix 4). The steps in the medicines approval system were examined as to when the potential failure modes could be observed in the procedure. The highest number of potential failure modes (n=12) that could be observed was identified to be during the evaluation of the Schedule V application by the POYC officer, while the least (n=1) could be observed during the first step when a patient consults a prescriber. Potential failure modes could also be observed when an authorised prescriber fills out the Schedule V application form (n=8), and when the patient submits the Schedule V application and/or supporting documents to POYC–MAS for evaluation (n=4).

Case descriptions for each of the potential failure modes were identified to ensure that each panelist had proper contextual meaning as to what is being referred in a particular potential failure mode (Appendix 5).

The grading scales and operational definitions for Severity, Occurrence, and Detectability were finalised by the panel as five-point ordinal scales, with a score of 5 indicating the highest degree of Severity and Occurrence, and the lowest degree of Detectability (Appendix 6). The panel adapted the risk matrix from the study of Lago et al (2012) on the reduction of risk of errors in prescribing and administering drugs in paediatric wards. The risk matrix utilised the product of Occurrence and Detectability as the x-axis, and Severity as the y-axis, with risks stratified as either critical (red; RPN = 44 to 125), high

(orange; RPN = 25 to 50), moderate (yellow; RPN = 4 to 30), or minor (green; RPN = 1 to 15) as in Figure 3.9. Overlaps in the ranges of the RPN could be observed, with having greater bearing on the Severity component considered in the preparation of the risk matrix to address the mathematical limitation of RPNs in which estimates for Severity, Occurrence, and Detectability were given equal weights. For example, a potential failure mode with a Severity of 4 and Occurrence x Detectability product of 12 (RPN = 48) will be considered as a critical risk, while a potential failure mode with a Severity of 2 but an Occurrence x Detectability product of 24 (RPN = 48) will be considered as high risk only. A greater area and RPN range for the critical risks were further considered for patient safety, and in anticipation that RPNs tend to pool at the lower end of the 1 to 125 scale (Gargama and Chaturvedi, 2011).

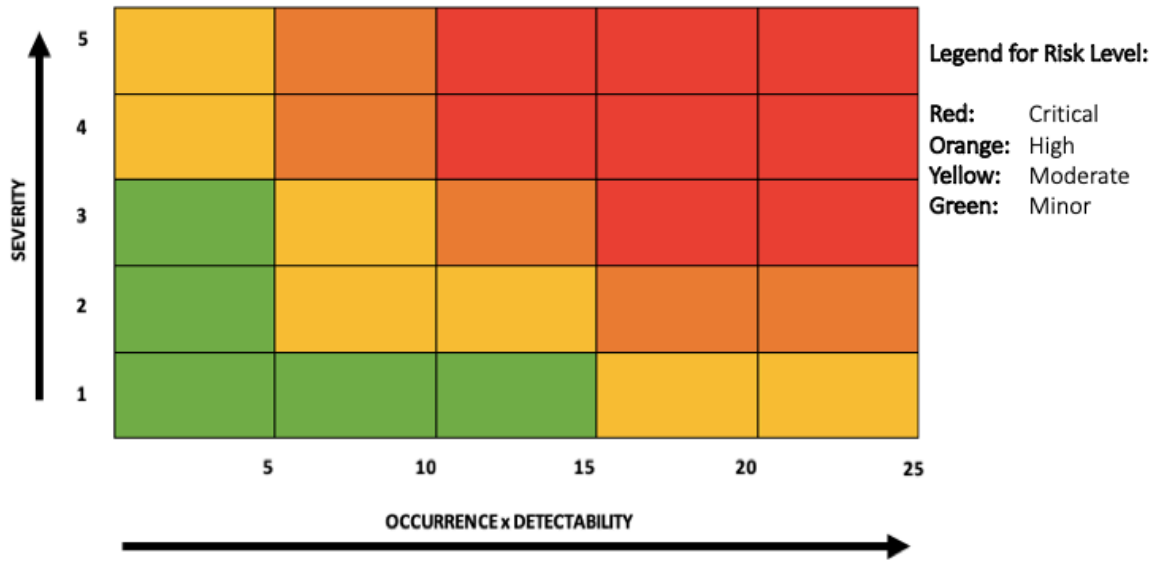


Figure 3.9. Risk matrix for the potential failure modes

After the first and second rounds of Delphi, the rounded-off scores of the mean values for Severity, Occurrence, and Detectability were used as the final scores in the FMEA, with 5 being the highest score for each of the variables. The scores for Severity, Occurrence, and Detectability were multiplied with each other to determine the RPN of the potential failure modes, obtaining a maximum score of 125 (Appendix 7). The total process RPN for the POYC medicines approval system was calculated by adding the RPNs of each of the potential failure modes, and was determined to be 874, out of a maximum of 3,125.

The five potential failure modes with the highest RPNs were: application was not according to government protocol (RPN = 100), medicine did not correspond to Schedule V condition (RPN = 60), application was awaiting for DPA approval for exceptional cases (RPN = 60), foreign patients failed to bring supporting documents to confirm eligibility to Schedule V scheme (RPN = 48), wrong prescriber criteria (RPN = 48).

The potential failure modes with least RPNs, and with values less than 25, were: prescriber did not apply for Schedule V (RPN = 24), prescriber's signature not recognisable nor legible (RPN = 24), prescriber did not complete patient information (e.g. name, ID number, address, date of birth) for access and confirmation (RPN = 24), prescriber applied for a condition that is not considered under Schedule V (RPN = 24), medicine listed not legible (RPN = 24), prescriber did not sign application form (RPN = 18), medicine is for in-patient use only (RPN = 18), prescriber did not tick nor indicate Schedule V condition or diagnosis in the application form (RPN = 18), and prescriber used the wrong form (RPN = 16).

The scores for Severity, Occurrence, and Detectability for each of the potential failure modes were plotted in the risk matrix to stratify and prioritise risks whether they are critical, high, moderate, or minor (Appendix 8). Five potential failure modes were identified as critical risks, 13 were high risks, 7 were moderate risks, and with none considered as minor risk. The critical risks which would need the highest priority in the Phase 3 of the research were the same as the items with the highest RPNs: (a) application was not according to government protocol, (b) medicine did not correspond to Schedule V condition, (c) application was awaiting for DPA approval for exceptional cases, (d) foreign patients failed to bring supporting documents to confirm eligibility to Schedule V scheme, and (e) wrong prescriber criteria.

3.8 Mapping of preliminary interventions suggested by FMEA Delphi panel

Based on the critical risks identified in Phase 2, the FMEA Delphi panel has identified pharmacist interventions which could be implemented to streamline access to approval of medicines (Table 3.6). These interventions were mapped to each of the potential failure modes (Appendix 9). Common intervention themes were the (a) development of orientation manual for prescribers and community pharmacists, (b) extensive and pro-active roll-out of online applications through the Centralised Aid for Repository Entitlement (CARE), an online portal through which prescribers can apply for Schedule V, (c) implementation of a feedback system between POYC, DPA, prescribers, and community pharmacists, (d) regular protocol and formulary review based on non-approval data, and (e) linking of POYC with other government databases for accessibility of foreign patient documentations. Extensive information dissemination among patients, availability of a dedicated coordinator for special entitlement cases, use of printed labels for patient details to reduce errors, and an increase in staff complement and office space were also suggested by the panel.

Table 3.6. Mapping of common intervention themes for the critical risks in the POYC-MAS potential failure modes

Potential Failure Modes	Interventions						
	Orientation Manual	Online Applications	Feedback System	Formulary and Protocol Review	Database Linking	Information Drive	Others
Critical Risks							
4.7 Application was not according to protocol			✓	✓			
4.10 Application was awaiting approval from the Directorate of Pharmaceutical Affairs (DPA) for exceptional cases	✓		✓	✓		✓	
4.4 Medicine did not correspond to Schedule V condition		✓	✓				
4.3 Wrong prescriber criteria		✓	✓				
3.3 Foreign patient failed to bring supporting documents (for example, payslip, COE, pension slip) to confirm eligibility in the scheme	✓				✓	✓	

3.9 Interventions targeted to streamline access to approval of Schedule V applications

Based on the FMEA and interventions identified by the panel, a detailed and tailored interview guide was prepared. The guide covered the specifics for the implementation of the interventions targeting critical risks in the POYC medicines approval system (Appendix 3).

A virtual meeting and interview was held with the Responsible Person of POYC to discuss the key interventions preliminarily identified from Phase 2. The contents for the orientation manual for prescribers and community pharmacists were identified, with the objective of allowing other stakeholders, particularly those at the start and end points of the distribution of free pharmaceuticals, to familiarize themselves with the POYC medicines approval system. The POYC-MAS officers should be tasked to prepare the orientation manual, with the following contents:

A. POYC Medicines Approval Process
B. Roles of POYC Officers, Prescribers, and Community Pharmacists
C. Government Formulary List and Protocols
D. CARE: Schedule V Online Application Software
E. POYC Schedule V Processes
    - Application for Schedule V
    - Application for Protocol-regulated Items
    - Application for Exceptional Medicines Treatment
    - Application for Open Treatments
    - Registration of Patients to POYC Scheme

- Registration of Prescribers
- Eligibility Requirements for Foreign Patients

The extensive and pro-active roll-out of online applications via CARE among authorised prescribers were identified by the key informant to benefit the medicines approval system by expediting the steps in the approval process, reducing patient traffic, reducing paper consumption, and providing real-time feedback to authorised prescribers regarding their Schedule V applications. The requirement for manpower to accommodate the influx of online CARE applications may be offset by redirecting POYC-MAS officers currently evaluating paper-based applications into processing online CARE applications. Assistance should be sought from the Office of the Chief Executive Officer of MDH in disseminating the orientation manual and encouraging hospital prescribers to lodge Schedule V applications via CARE.

A standard operating procedure should be drafted by the Client Support System or Technical Human Resource of POYC for the monthly or quarterly summary data on non-approvals for dissemination among authorised prescribers, community pharmacists, and DPA. The objective is to allow the stakeholders to be informed of the decision-making happening at the point of evaluating Schedule V applications. It is considered ideal that feedback regarding patient-specific Schedule V applications be forwarded via a CARE feature to the authorised prescribers and community pharmacists to address problems arising from the patient's lack of understanding of the POYC medicines approval process. Feedback coming from authorised prescribers and community pharmacists, which is currently relayed through emails, must also be made possible through CARE.

While formulary and protocol review are outside the remit of POYC, individual patient needs and concerns regarding formulary and protocol restrictions were raised for appropriate evaluation and action of DPA in the past. The linking of POYC with other government databases to facilitate access to supporting documents required for approval of Schedule V applications should be worked on by the Information Technology personnel of POYC, through the guidance of the Data Protection Officer to ensure patient confidentiality.

The main outcome measure that can be used to determine the overall success of the interventions is the percentage annual reduction of non-approvals, as identified by the key informant. The number of authorised prescribers utilising CARE, number of online CARE applications, and stakeholder satisfaction were identified as secondary outcome measures which are specific to each of the interventions.

Chapter 4

Discussion

4.1 Occurrence of delay in access to care

As per the Preamble to the Constitution of World Health Organization (WHO), "Health" is defined as the state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity.[58] The determinants of health would factor in the social, economic, and physical environment, and a person's individual' characteristics and behaviors to identify the health of a society.[59]

Given that an individual person would most likely cannot directly control some of the determinants of health, a nation's government should be able to build a healthcare system which centers on reducing the gaps between its constituents while respecting their rights and personal circumstances.[60] Generally, the health goals of any health system may be identified through a political process, resulting in the following broad categories: reducing mortality, reducing morbidity, reducing health inequalities, improving outcomes for a particular disease, or making health care safer (Bengoa et al., 2006). Improving a social determinant like health services, especially those managed by a government, would be one of the means of achieving any of the health goals of a health system (Tang et al., 2004).

[58] World Health Organization. Constitution [Internet]. WHO; 2021 [cited 2021 May 14]. Available from URL: https://www.who.int/about/who-we-are/constitution

[59] NEJM Catalyst. Social Determinants of Health (SDOH) [Internet]. Massachusetts; 2017 [cited 2021 May 14]. Available from URL: https://catalyst.nejm.org/doi/full/10.1056/CAT.17.0312

[60] Commission on Social Determinants of Health. Closing the gap in a generation: health equity through action on the social determinants of health. Final Report of the Commission on Social Determinants of Health [Internet]. World Health Organization; 2008 [cited 2021 May 14]. Available from URL: https://www.paho.org/hq/dmdocuments/2013/Social-Determinants-of-Health-WHO-2008-Commision-on-Final-Report-eng.pdf

In Malta, one of the most prominent health services is the POYC, as it is responsible in ensuring equitable accessibility to its government's free pharmaceutical services in a timely, accurate, and efficient manner. The mandate of POYC has also been aligned with the National Health Systems Strategy of Malta in ensuring that an accessible health service is implemented and continuously upgraded, especially that Malta's economic growth is dependent on the health of its entire population.[61] Hence, it is necessary that process improvements are in place within POYC to ensure that its objectives are constantly being met.

The Andersen's General Model of Total Patient Delay describes types of delays which could ultimately impact timely and efficient access to care: (a) appraisal delay or the point at which a patient recognises a symptom as a marker of illness, (b) illness delay or the period covering a patient's first sign of illness until their decision to seek professional medical help, (c) behavioral delay or the period between making the decision to seek care and acting on it, (d) scheduling delay or the time between acting on the decision and actually attending a health appointment, and (e) treatment delay or the time lag from diagnosis of a disease to the first initiation of treatment (Bello et al., 2019; Walter et al., 2012). Ensuring timely and efficient access to care by reducing treatment delays were found to not only reduce clinically-associated outcomes such as pain, anxiety, disability, and death, but to also increase the economic value of care provided through clinical services (Richard et al., 2018; Heinrich et al., 2018), thereby benefitting both the government and its citizens.

[61] Ministry for Energy and Health. A National Health Systems Strategy for Malta 2014 – 2020 [Internet]. Malta: Ministry for Energy and Health; 2014 [cited 2021 May 14]. Available from URL: https://deputyprimeminister.gov.mt/en/Documents/National-Health-Strategies/NHSS-EN.pdf

The impact of reducing delays in treatment would greatly be felt by the most vulnerable populations, which would include those with chronic illnesses, the financially-challenged, and the elderly (DiMatteo, 2004; Prentice and Pizer, 2007). Improving access to treatment would be considered highly-relevant in Malta as a cost-containment measure, in consideration that an increase in health expenditure is forecasted due to the ageing and growing Maltese population.[62]

An aspect of POYC that could be examined for process improvements is the medicines approval system. While the system has been implementing process controls in the form of formulary, protocol, and policy reviews over the past few years, as evidenced by the constant decrease in non-approvals from 2012, a total of 36108 non-approvals were still recorded with a portion due to preventable causes which are structural in nature. Such figures of non-approvals would merit attention and necessary action as delaying access to certain medicines may impact clinical, economic, and humanistic outcomes. Treatment delays were found to result in a decrease in quality of life (Chen et al., 2011) and response to treatment (Drake et al., 2020), increase in mortality (Comber et al., 2005; Rivero et al., 2016; Hanna et al., 2020; Maringe et al., 2020) and morbidity rates (Moser et al., 2006), and higher hospitalisation costs (Kraft et al., 2009; Haque, 2020).

[62] Organisation for Economic Cooperation and Development/European Observatory on Health Systems and Policies. State of Health in the EU: Malta Country Health Profile 2019 [Internet]. OECD; 2019 [cited 2021 May 14]. Available from: https://www.euro.who.int/__data/assets/pdf_file/0005/419468/Country-Health-Profile-2019-Malta.pdf

In relation to POYC non-approvals, it is important to understand what courses of action are available to the patient in order to access their treatment. A patient may either (a) return to their prescribers to re-evaluate the need for an alternative, or for another Schedule V application in the context of POYC, (b) buy the medicine through out-of-pocket expenses, or (c) decide not to take the medicine due to financial incapacity or inconvenience. A patient's decision to persist in seeking care despite the presence of many factors contributing to treatment delays may be summarised using the consultation theory by Becker and Maiman (1970s) called the Health Belief Model.

The Health Belief Model is used to involve processing personal beliefs and experiences from the patient's point of view, to elicit a personal plan of care (Figure 4.1). A patient's likelihood of taking recommended action, which is to either buy medicine through out-of-pocket expenses or buy an alternative despite non-approval of entitlement, is influenced by factors such as individual and modifiable perceptions, demographic, socio-psychological, and structural variables, and cues to action.[63] Variables specific in the context of POYC would include the structural process as to how Schedule V applications are being evaluated, and approved, and what are the triggers to a patient's action, inclusive of experiences shared by relatives or friends regarding POYC, advice from others, online information campaigns organised by POYC, and special situations like the COVID-19 pandemic. Other modifying factors inherent to the patients would include age, sex, race, personality, social class, disease knowledge, and personal health beliefs.

[63] Health Communication Capacity Collaborative. Health Belief Model [Internet]. Johns Hopkins University; 2017 [cited 2021 May 14]. Available from URL: https://sbccimplementationkits.org/quality-malaria-medicines/health-belief-model/

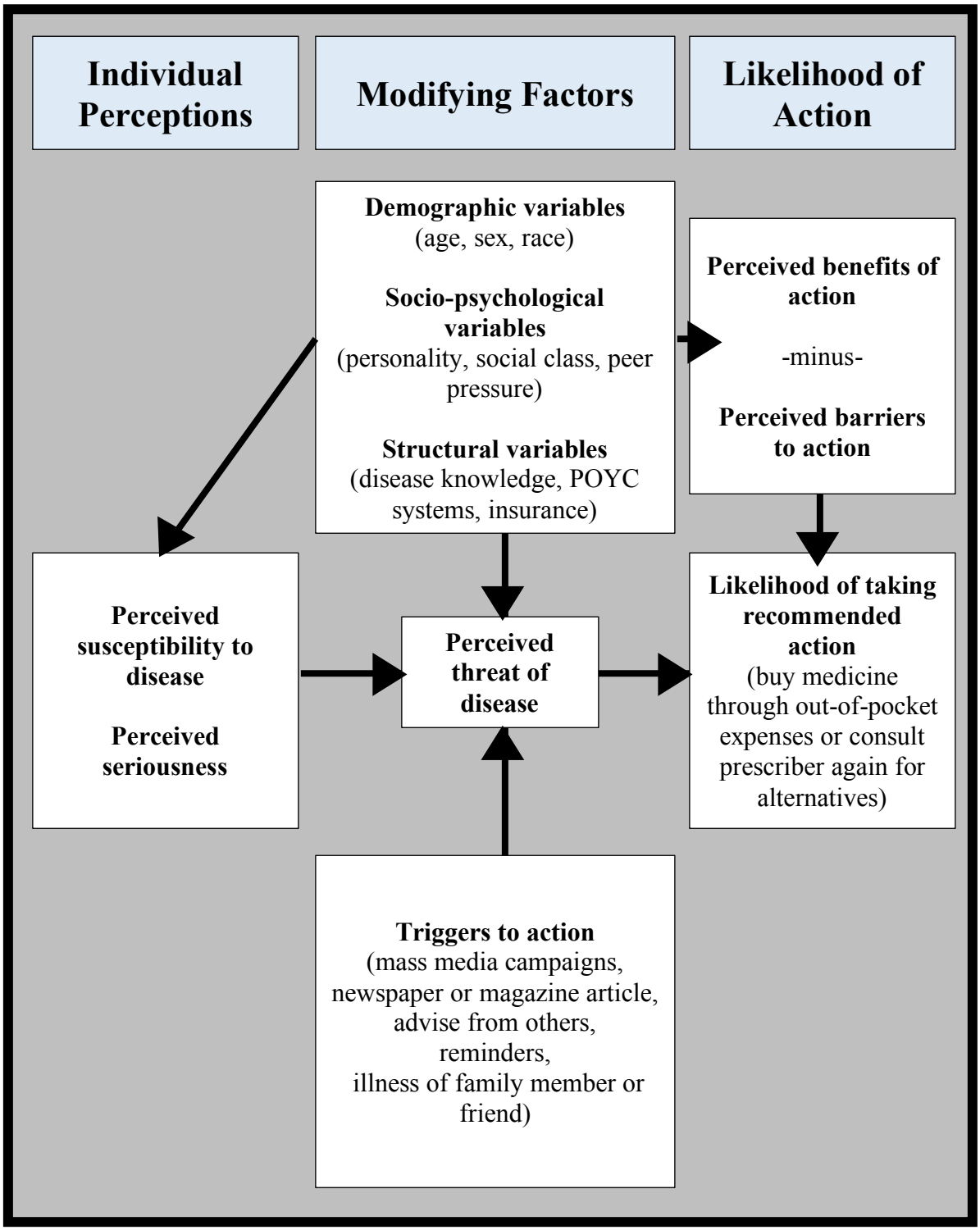


Figure 4.1. Factors affecting POYC treatment delays diagrammed using the Health Belief Model

The COVID-19 pandemic has not only played a vital role among the patients, but it also influenced the POYC medicines approval system as a whole. The POYC medicines approval system showed volatility during the COVID-19 pandemic, with non-approvals in 2019 amounting to 1961 then doubling to 3951 for a shorter eight-month period in 2020. When the same six-month period in 2019 and 2020 were compared with each other, it was found that the monthly non-approvals during the COVID-19 pandemic were consistently higher as compared to the non-approvals recorded before the pandemic ($t=4.597$, $p=0.0025$).

The significant increase in the non-approval cases during the COVID-19 pandemic may be attributed to a process change wherein the POYC medicines approval system has been heavily-reliant on non-contact communication such as posts, emails, and phone calls as part of safety precautions against COVID-19. These changes could have decreased the amount and quality of communication between the prescribers, patients, and POYC officers, thereby decreasing opportunities to detect and relay reasons for non-approvals at the soonest time possible. Ratna (2019) has suggested that effective communication is critical within a health service, and that the delivery of care may be compromised when there is lack of effective communication between stakeholders. Apart from the negative impact, changes in the process may also bring positive effects in the form of increasing efficiency and productivity in the organisation (Feldmann, 2014). The pandemic has highlighted the importance of establishing an online information systems, CARE software in the case of POYC, which would ensure effective communication and increase employee productivity and performance. Implementation of the CARE software simplified the approval process by allowing prescribers to directly lodge Schedule V applications online and eliminating the need for paper documents and for patients to go back and forth different offices.

In ensuring an effective communication with patients, the Anthropological or "Folk" Model by Helman (1980s) may be used as a guidance. It states that patients seeking medical advice tend to be satisfied when certain questions are answered by healthcare professionals, even without the patient expressing them (Grimes and Barnett, 2014). Notifications and communications directed to patients regarding non-approvals must ensure that such questions are clearly addressed and explained. A detailed examination of the note being provided to patients as feedbacks regarding non-approvals (Appendix 1) showed that the questions can all be answered except: (a) What would happen if nothing was done? (b) What should I do about it? And (c) Who should I consult for further help? (Table 4.1).

Table 4.1. Examination of POYC non-approval note using the Anthropological Model

Questions in Anthropological Model	POYC Non-approval Note
A. What has happened?	Sufficiently answered using the statement "I would like to inform you that your Yellow Card application was not approved…"
B. Why has it happened?	Sufficiently answered using the table specifying which medicine has not been approved, alongside the row for the five general reasons for non-approval of Schedule V applications
C. Why has it happened to me?	
D. Why has it happened to me now?	
E. What would happen if nothing was done?	Lacked clear instructions to inform patient regarding non-approval consequences
F. What should I do about it?	Answered using the statement "Kindly talk to the Consultant to apply for a permit or Schedule V," but may be considered as lacking for situations when a medicine is not available on the GFL
G. Who should I consult for further help?	

It is recommended that the POYC non-approval note is further tailored to the Anthropological Model to ensure that patients would fully understand the consequences when a medicine is not approved, and to influence them to persist in seeking care to minimise possible delays in access to treatment. It has to be included in the POYC non-approval note that the non-approval would only mean that the medicine could not be provided by the government for free as per government legislations, and hence, does not mean that patients should not continue with the treatment.

The importance of ensuring the robustness and preparedness of a system during disasters and calamities through risk management has been highlighted as seen with the change in the POYC medicines approval system translating to twice the amount of non-approvals during the COVID-19 pandemic. In optimising the system, the proper identification and prioritisation of risk areas is important for the proper allocation of government resources. According to Gershengorn et al. in 2014, the Pareto Principle states that around 80% of the problem cases may arise from about 20% of the causes. Subsequently, focusing on solving the leading 20% of the causes may yield results affecting 80% of the problem cases. Based on the retrospective and Pareto analyses of POYC databases on non-approvals, it was found that 102 out of the 661 unique medicine-specific reasons and 5 out of the 21 process-specific reasons contributed to 80% of partial non-approvals, while there were 8 out of 21 process-specific reasons for full non-approvals.

The process-specific reasons for non-approvals which could be considered as preventable would include: (a) no MAS permit application, as prescribers could simply fill-out the protocol-regulated form to apply for MAS permits, (b) no supporting document as required by government protocol, as prescribers may reproduce the copy of the supporting document for the patient, (c) prescribers did not apply for Schedule V, and (d) patient failed to bring the original Schedule V application. Other process-specific reasons which may be considered as non-preventable as they are inherent to the role of POYC-MAS of filtering out applications not in line with government policies would include: (a) medicine not corresponding to a Schedule V condition, (b) application not according to the government protocol, (c) and medicine not available on the GFL.

It has to be emphasised that a process-specific reason that is not preventable would not necessarily mean that it would not require attention. Instead, a proper inquiry and evaluation must be made to understand further why such process-specific reasons occurred. For example, the DPA through POYC-MAS may develop a feedback system wherein the medicines not corresponding to a Schedule V condition be further characterised. This would allow the unit of formulary management in DPA to be informed of the on-ground data on the demands of the Maltese population. The same may also be performed when investigating which medicines are not yet available on the formulary, but have already precipitated requests from both prescribers and patients for free provision.

4.2 Risks associated with delay in access to care

The Pareto analysis has identified the priority reasons for non-approvals based on the data on their occurrence. It is also equally important to evaluate these reasons for non-approvals in terms of the degree as to how they may impact the health of the patient, and as to how the POYC medicines approval system can detect and prevent such reasons from occurring. One risk assessment tool that can analyse risks in the POYC medicines approval system based on severity, occurrence, and detectability is FMEA. Through this tool, a systematic inquiry on the risks associated with non-approvals was performed by incorporating objective information on the occurrence of non-approvals, together with the subjective data assessed by a panel of members with extensive knowledge and experience on the POYC medicines approval system. An extensive view of the risks associated with non-approvals was targeted by ensuring that the panel composition would be reflective of the feedback coming from the different sectors involved in the POYC medicines approval system – hence the participation of a community pharmacist with experience on dealing with patients whose medications were not approved, an authorised prescriber with a background on applying for Schedule V documents on behalf of the patient, and two POYC officers in-charge of processing online CARE applications and receiving feedback regarding EMT requests from DPA.

Based on the FMEA, almost half of the potential failure modes could be observed during the evaluation of the Schedule V application by the POYC officer. This would mean that appropriate process controls must be in place specifically in this step, to allow for the detection and prevention of the potential failure modes from occurring. For example, the

implementation of a double-checking procedure in the preceding steps by both the prescriber and the patient may prevent potential failure modes from happening at the later stage of the approval process. This intervention would prevent prescribers from not filling out the Schedule V condition in the application form, or from not reinforcing to the patient the need to attach supporting documents required by a government protocol. In another case, automating the POYC medicines approval system may prevent problems with illegible handwriting in the Schedule V application form and may provide immediate feedback whether the medicine is not available on the GFL, if it is for in-patient use that is not covered by POYC, or if it does not correspond to a Schedule V condition, thereby reducing the steps that a patient has to go through before realising that they may not be entitled to a certain medicine. Benefits which could arise from this intervention may also include reduction in the workload among prescribers, patients, and POYC officers, provision of a level of stability and certainty when applying for Schedule V, and reduction in the occurrence of human errors (Breton and Bosse, 2003). The implementation of such process controls are mechanisms which also directly influence the risk level associated with the POYC medicines approval system (Nolan, 2011).

A more comprehensive information could be derived from examining the RPNs and risk matrix for the potential failure modes. While the RPN puts equal bearing between the severity, occurrence, and detectability of a potential failure mode due to the scores being arbitrarily scaled at a maximum score of 5 for each of the RPN components, the risk matrix was prepared to reflect bigger emphasis on the severity of a potential failure mode. For example, there are two potential failure modes both with an RPN of 48, the first one has a severity of 2, occurrence of 5, and detectability of 5, while the other has a severity of 5,

occurrence of 2, and detectability of 5, then the latter would be categorised as critical risk (red zone), as compared to the former which would be categorised as high risk (orange zone) using the risk matrix. The rationale for such decision in the context of this research was that it would be harder to remedy failure modes which have caused a more severe health impact to a patient, than planning to reduce the likelihood of a potential failure mode from occurring.[64]

Several potential failure modes categorised as critical risks were: application was not according to government protocol (RPN = 100), medicine did not correspond to Schedule V condition (RPN = 60), application was awaiting for DPA approval for exceptional cases (RPN = 60), foreign patients failed to bring supporting documents to confirm eligibility to Schedule V scheme (RPN = 48), wrong prescriber criteria (RPN = 48), and the total process RPN for the POYC medicines approval system was determined to be 874. The general course of action for critical risks would involve reassessment and development of process controls targeted to mitigate its negative effects in the POYC medicines approval system.

For the medicine-specific reasons for non-approvals, clopidogrel (8%), levothyroxine (5%), omeprazole (4%), vitamins (unspecified, 3%), atorvastatin (3%), valsartan/candesartan (3%), folic acid (2%), lactulose (2%), oral iron (2%), and ipratropium (2%) were shown to contribute the highest in the cases. Case studies were prepared for clopidogrel, levothyroxine,

[64] Buthmann A. Use a modified FMEA to mitigate project risks [Internet]. ISIXSIGMA; 2020 [cited 2021 May 14]. Available from URL: https://www.isixsigma.com/tools-templates/fmea/use-modified-fmea-mitigate-project-risks/

and omeprazole to distinguish whether the delays in their respective approvals would cause harm, or if a more lenient GFL or protocol criteria would benefit more patients.

Based on the case studies, it would be more acceptable that clopidogrel is ensured to be given to patients requiring it, in view of risks of secondary myocardial infarction, death, and higher health-related costs when prematurely discontinuing upon hospital discharge by reviewing the process of access to clopidogrel approvals (Kubica et al., 2016; Mauri et al., 2016; Elmariah et al., 2018; Luu et al., 2019). The estimated mean treatment costs for myocardial infarction were at € 5,021, with PCI contributing largely in the increase in cost, and the length of stay and type of hospital as the strongest predictors (Soekhlal et al., 2013). This could mean that three failed attempts to prevent a secondary atherothrombotic events, specifically myocardial infarction, would already offset the annual cost for providing clopidogrel to 1,925 entitled patients in the Schedule V scheme. A modest risk of gastrointestinal adverse events associated with clopidogrel use was recorded (Grove et al., 2013), and the mean in-hospital costs for patients admitted with acute upper gastrointestinal bleeding due to clopidogrel was estimated to be at £ 2,458 (€ 2,854), with inpatient bed days, blood transfusion, and endoscopy as the key cost drivers (Campbell et al., 2015).

It is recommended to re-evaluate the formulary mapping for levothyroxine given that bulk of the levothyroxine non-approvals were due to Schedule V conditions in which levothyroxine is not currently mapped under. It has to be noted that patient safety must not be compromised by urging prescribers to weigh the risks and benefits of using levothyroxine on a case-to-case basis, thereby preventing unnecessary use resulting in patients experiencing

irregular heartbeat, insomnia, and loss of bone density, without receiving any beneficial effect from it.[65]

Healthcare professionals are also being urged to re-confirm the necessity of prescribing omeprazole to patients by ensuring that the benefits would outweigh the potential harms (Kinoshita et al., 2018) including diarrhea (Shimura et al., 2012), acute interstitial nephritis (Berney-Meyer et al., 2014), and increased risks of cerebral and cardiac ischaemic attacks (Wang, 2017; Xie, 2017), and pneumonia (Sarkar et al., 2008; O'Neill et al., 2013). As guidance, the overall costs for GORD and peptic ulcer disease were estimated to be at around € 253 (Mahmood and McNamara, 2003), while increase in hospitalisation costs amounting to $ 15,682 (€ 12,863) were observed among patients with pneumonia due to inappropriate use of omeprazole (O'Neill et al., 2013). It is recommended that the appropriateness of use of omeprazole, even after approval, is re-evaluated through drug utilization reviews, not only to ensure patient safety, but as a cost-saving measure given the high spending for the actual patient entitlements, and possible costs due to its inappropriate use.

4.3 Optimisation of approach to reduce delay in access to care

Pharmacists can develop interventions in the area of medicines approval system to contribute in ensuring timely access to medicinal entitlements, thereby optimising health

[65] Godman H. For borderline underactive thyroid, drug therapy isn't always necessary [Internet]. Harvard Health Publishing; 2019 [cited 2021 May 14]. Available from URL: https://www.health.harvard.edu/blog/for-borderline-underactive-thyroid-drug-therapy-isnt-always-necessary-201310096740

outcomes. The interventions may be in the form of improving health information technology and access to care, as pointed out by The Joint Commission (2015).[66]

Interventions targeted to streamline access to approvals by addressing mainly the critical risks in the POYC medicines approval system were developed by pharmacists, in collaboration with pharmacy technicians and prescribers. These could be divided into two major areas: (a) improvement of health information technology, and (b) improvement of access to care. The latter would involve regular protocol and formulary review by DPA, as guided by the data on non-approvals collected by POYC monthly.

Investing on health information technology such as order entries, clinical decision support, and automated notes in the hospital setting have resulted in benefits in the form of decrease in mortality rates, decrease in the risk of complications, and decrease in the risk of fatal hospitalisations (Bates, 2018). In a general setting, the use of information technology presents opportunities to improve quality and availability of health services, as well as to solidify concepts of patient empowerment and seamless transitions in care (Duplaga, 2004). In the context of POYC, the following interventions fall under this area: (a) development of orientation manual for prescribers and community pharmacists, (b) extensive and pro-active roll-out of online applications through CARE, (c) implementation of a feedback system between POYC, DPA, prescribers, and community pharmacists, and (d) linking of POYC

[66] The Joint Commission. Preventing delays in treatment. Quick Safety (Issue Nine) [Internet]. Division of Health Care Improvement [cited 2021 May 14]. Available from URL: https://www.jointcommission.org/-/media/deprecated-unorganized/imported-assets/tjc/system-folders/joint-commission-online/quick_safety_issue_nine_jan_2015_finalpdf.pdf?db=web&hash=D5C49298D4FCB08F66F710FDFFD8CFC3

with other government databases for accessibility of foreign patient documentations and health records.

The development of an orientation manual allows prescribers and community pharmacists to understand the POYC medicines approval system. This also serves as a short form of induction training for newly-authorised prescribers such that potential failure modes arising from the start of the approval process would be prevented using the orientation manual as a reference guide.

The coverage for the roll-out of online CARE applications must also be increased as this intervention could target numerous potential failure modes, with the advantage of decreasing paper consumption and personal contact, especially in view of the COVID-19 pandemic. Apart from targeting critical risks, online applications would also prevent the following non-critical risks by providing real-time feedback to the applying prescriber: (a) prescriber wrote the wrong patient information, (b) prescriber not eligible to apply for Schedule V or permit, (c) prescriber did not apply for Schedule V, (d) prescriber's signature not recognisable nor legible, (e) prescriber did not complete patient information (e.g. name, ID number, address, date of birth) for access and confirmation, (f) prescriber applied for a condition that is not considered under Schedule V, and (g) medicine listed not legible, among others.

The implementation of feedback system between POYC, DPA, prescribers, and community pharmacists would allow the tailoring of the POYC medicines approval system based on the actual experiences of the stakeholders. It is envisioned that POYC provides

monthly feedback to DPA, prescribers, and community pharmacists regarding data on non-approvals to immerse stakeholders as to what is occurring within POYC. Prescribers and community pharmacists are encouraged to participate in the optimisation process of the POYC medicines approval system through their suggestions and reports regarding patients using the service.

Linking of POYC with other government databases would allow ease in confirming eligibility of foreign patients in the Schedule V scheme, instead of requesting eligibility documents during each time a new application is received from their end. In this intervention, requests for copies of national insurance contributions and pension slips may be connected with the Social Security department, COEs through the Entitlement Unit Healthcare Funding Directorate of the Ministry for Health, marriage certificates involving Maltese citizens through the Public Registry Office, and refugee certificates from the Office of the Refugee Commissioner. Access to patient health records available through MDH and government health centres, with the consent of the patient, could also be made available for easier access to common information required by government protocols for issuance of MAS permits: LDL report for Rosuvastatin, PCI/TAVI report or case summary for Clopidogrel, form D1 showing MMSE score for Donepezil, duodenal biopsy report for gluten-free diet vouchers for Coeliac patients, and HbA1c report for Vildagliptin. This is envisioned to address problems with clopidogrel in which one of the common process-specific reasons for non-approvals has been the lack of supporting document required by the government protocol.

4.4 Limitations of the study

The study has involved a retrospective analysis of database from 2012 to 2020, and the accuracy of data has been assumed in consideration that data collection controls could only be set at the time of retrieval of information from the database. While the study was able to quantify the frequency counts of non-approvals, the data on the proportion of patients eventually receiving approvals for previously non-approved entitlements was not collected since the process of recording non-approvals at POYC-MAS did not include such information. This further resulted with the lack of information as regards the length of delay a patient experienced before accessing approvals to their entitlements.

The analysis involving COVID-19 pandemic and its relationship with non-approvals only involved a six-month period at the start of the pandemic. A longer timepoint may be warranted to further ensure that statistical analyses to be performed are robust and powerful.

Case studies on the top medicine-specific reasons for non-approvals used a generalist approach, and have disregarded patient-specific factors such as demographics, social factors, and comorbidities which may directly influence response of patient to use, misuse, and non-adherence to the medicinal subjects of the case studies.

For FMEA, the prescriber involved in the Delphi panel may only reflect the personal experiences specific to their area of specialisation. This is particularly important since the POYC medicines approval system heavily depends on the prescriber specialisation criteria. The involvement of prescribers from varying background and specialisation may provide a

more holistic view of the risks associated with non-approvals. The grading scales for severity and detectability were subjectively agreed upon by the Delphi panel. This may under- or over-estimate the actual values for these variables as compared when a much rigorous deliberation and validation process is used in developing such grading scales. It has to be noted that the grading scales used were in the ordinal level of measurement, indicating that a score of 2 in severity would not mean twice the level of another potential failure mode with a score of 1. The same is also true with RPNs, wherein a potential failure mode with an RPN of 60 would not be equivalent to twice the risk of a potential failure mode with an RPN of 30.

4.5 Recommendations for further study

Further studies are recommended to quantify the duration of delay in access to treatment due to non-approvals in the POYC medicines approval system. The results would provide more valuable information regarding the severity of impact of non-approvals.

A time-motion study on the approval process may also reflect better information on the detectability of potential failure modes and the time spent by stakeholders when applying, evaluating, and approving Schedule V applications.

Further case studies on clopidogrel, levothyroxine, and omeprazole may also be conducted with actual consideration of patient-specific factors for better decision-making regarding the GFL and protocol specifications governing their approvals, and its pharmacoeconomic implications.

Studies on the effect of pharmacist interventions proposed are recommended to visualise the extent of optimisation of the POYC medicines approval system. This study should involve the implementation of the interventions and evaluation through repeat-FMEA to identify whether there are reductions in the RPNs of the potential failure modes, as well as changes in the risk classification. Further studies on the clinicalisation of the medicines approval process may pave the way for the involvement of POYC pharmacists to conduct drug utilization review and medication therapy management.

4.6 Conclusion

The study was able to characterize the reasons for non-approval of Schedule V applications by providing information on the medicine-specific and process-specific causes serving as bottlenecks in the POYC medicines approval system, before and during the COVID-19 pandemic. A Pareto analysis of these reasons for non-approvals showed that the majority of the cases of non-approvals were caused by the few high-impact medicine-specific (clopidogrel, levothyroxine, and omeprazole) and process-specific reasons (medicine not corresponding to the Schedule V condition, application not according to government protocol, and medicine not available on the GFL).

In view of the COVID-19 pandemic, it can be concluded that the mean non-approvals before the pandemic was significantly lower as compared to during the pandemic ($t=4.597$, $p=0.0025$). The study was able to identify a process change to facilitate non-contact communication in the POYC medicines approval system and the lack of tailored feedback being disseminated to patients as the factors contributing to the increase in the mean non-approvals during the pandemic.

The case studies on the top medicine-specific reasons could be used as a guidance for the interventions to lower non-approvals, while ensuring appropriate use. Clopidogrel must be ensured to be given to patients requiring it, in view of risks of secondary myocardial infarction, death, and higher health-related costs when prematurely discontinuing upon hospital discharge. Healthcare professionals should be urged to re-confirm the necessity of

prescribing levothyroxine and omeprazole to patients by ensuring that the benefits would outweigh the potential harms.

The risks associated with non-approvals were also evaluated using FMEA and a risk matrix. By using the data on the severity, occurrence, and detectability of the potential failure modes, RPN values were calculated to visualise how one potential failure mode would need prioritisation over the other. Potential failure modes categorised as critical risks were: application was not according to government protocol (RPN = 100), medicine did not correspond to Schedule V condition (RPN = 60), application was awaiting for DPA approval for exceptional cases (RPN = 60), foreign patients failed to bring supporting documents to confirm eligibility to Schedule V scheme (RPN = 48), wrong prescriber criteria (RPN = 48), and the total process RPN for the POYC medicines approval system was determined to be 874. It is recommended that these critical risks be reassessed, with process controls targeted to mitigate its negative effects in the POYC medicines approval system be developed.

Pharmacist interventions were developed in view of improving the POYC medicines approval system, with the goal of efficiently allocating resources on interventions with the biggest impact in the system. These interventions ranged from developing orientation manuals for prescribers and community pharmacists, to rolling-out of online applications through CARE, and to implementing a feedback system between the stakeholders of POYC.

References

Bates DW. The Effects of Health Information Technology on Inpatient Care. Archives of Internal Medicine. 2009;169(2):105-107.

Bello S, Afolabi RF, Ajayi DT, Sharma T, Owoeye DO, Oduyoye O, et al. Empirical evidence of delays in diagnosis and treatment of pulmonary tuberculosis: systematic review and meta-regression analysis. BMC Public Health [Internet] 2019 [cited 2021 May 14] ;19(820). Available from URL: https://bmcpublichealth.biomedcentral.com/articles/10.1186/s12889-019-7026-4

Bengoa R, Kawar R, Key P, Leatherman S, Massoud R, Sturno P. Quality of care: A process for making strategic choices in health systems. World Health Organization Press. 2006:1-50.

Berney-Meyer L, Hung N, Slatter T Schollum JB, Kitching AR, Walker RJ. Omeprazole-induced acute interstitial nephritis: a possible Th1-Th17-mediated injury? Nephrology. 2014;19(6):359-365.

Bojovic O, Medenica M, Zivkovic D, Rakocevic B, Trajkovic G, Kisic-Tepavcevic D, et al. Factors associated with patient and health system delays in diagnosis and treatment of tuberculosis in Montenegro. Public Library of Science [Internet] 2018 [cited 2021 May 14];13(3). Available from URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5844538/

Breton R, Bosse E. The Cognitive Costs and Benefits of Automation. North Atlantic Treaty Organization. 2003:1-2.

Campbell HE, Stokes EA, Bargo D, Logan RF, Mora A, Hodge R, et al. Costs and quality of life associated with acute upper gastrointestinal bleeding in the UK: cohort analysis of patients in a cluster randomised trial. BMJ Open [Internet] 2015 [cited 2021 May 14];5:e007230. Available from: https://bmjopen.bmj.com/content/5/4/e007230

Chen J, Rizzo JA, Hector HP. The Health Effects of Cost-Related Treatment Delays. American Journal of Medical Quality. 2011;26(4):261-271.

Comber H, Cronin DP, Deady S, Lorcain PO, Riordan P. Delays in treatment in the cancer services: impact on cancer stage and survival. Irish Medical Journal. 2005;98(8):238-9.

Daw JR, Morgan SG. Stitching the gaps in the Canadian public drug coverage patchwork? A review of provincial pharmacare policy changes from 2000 to 2010. Health Policy. 2012;104(1):19–26.

DiMatteo, MR. Variations in patients' adherence to medical recommendations: a quantitative review of 50 years of research. Medical Care. 2004;42(3):200-209.

Drake RJ, Husain N, Marshall M, Lewis SW, Tomenson B, Chaudhry IB, et al. Effect of delaying treatment of first-episode psychosis on symptoms and social outcomes: a longitudinal analysis and modelling study. The Lancet Psychiatry. 2020;7(7):602-610.

Duplaga M. The Impact of Information Technology on Quality of Healthcare Services. Springer-Verlag Berlin Heidelberg. 2004:1118-1125.

Elmariah S, Doros G, Benavente OR, Bhatt DL, Connolly SJ, Yusuf S, et al. Impact of Clopidogrel Therapy on Mortality and Cancer in Patients With Cardiovascular and Cerebrovascular Disease: A Patient-Level Meta-Analysis. Circulation: Cardiovascular Interventions [Internet] 2018 [cited 2021 May 14] ;11:e005795. Available from URL: https://www.ahajournals.org/doi/10.1161/CIRCINTERVENTIONS.117.005795

Feldmann TB. Understanding the Dynamics of Change and the Impact on Psychiatric Education. Academic Psychiatry. 2014;(38):672–679.

Fenech J, Azzopardi LM. Pharmacy of Your Choice scheme and management of hypertension. Journal of Euromed Pharmacy [Internet] 2013 [cited 2021 May 14] ;03:17-20. Available from URL: https://www.um.edu.mt/library/oar/bitstream/123456789/41212/1/Pharmacy_of_Your_Choice_scheme_and_management_of_hypertension_2013.pdf

Gargama H, Chaturvedi SK. Criticality Assessment Models for Failure Mode Effects and Criticality Analysis using Fuzzy Logic. IEEE Transactions on Reliability 2011;60(1):102-110.

Gershengorn HB, Kocher R, Factor P. Management Strategies to Effect Change in Intensive Care Units: Lessons from the World of Business: Part I. Targeting Quality Improvement Initiatives. Annals of the American Thoracic Society. 2014;11(2):264-269.

Gorener A, Toker K. Quality Improvement in Manufacturing Processes to Defective Products using Pareto Analysis and FMEA. Beykent University Journal of Social Sciences [Internet] 2013 [cited 2021 May 14] ;06(02). Available from URL: https://dergipark.org.tr/tr/download/article-file/482107

Grimes L, Barnett N. Consultation skills for pharmacy practice: taking a patient-centred approach. Manchester: Outset Publishing Ltd.; 2014. p. 46-47.

Grove EL, Würtz M, Schwarz P, Jørgensen NR, Vestergaard P. Gastrointestinal events with clopidogrel: a nationwide population-based cohort study. Journal of General Internal Medicine. 2013;28(2):216-222.

Guzman IB, Cuesta JG, Trelles M, Jaweed O, Cherestal S, Frank van Loenhout JA, et al. Delays in arrival and treatment in emergency departments: women, children and non-trauma consultations the most at risk in humanitarian settings. Public Library of Science [Internet] 2019 [cited 2021 May 14] ;14(3). Available from URL: https://journals.plos.org/plosone/article/file?id=10.1371/journal.pone.0213362&type=printable

Hanna TP, King WD, Thibodeau S, Jalink M, PaulinG A, Harvey-Jones E et al. Mortality due to cancer treatment delay: systematic review and meta-analysis. British Medical Journal [Internet] 2020 [cited 2021 May 14] ; 371:m4087. Available from URL: https://www.bmj.com/content/371/bmj.m4087

Haque LA. The Effect of Delays in Acute Medical Treatment on Total Cost and Potential Ramifications due to the Coronavirus Pandemic. Harvard Public Health Review [Internet] 2020 [cited 2021 May 14] ;26. Available from URL: https://harvardpublichealthreview.org/delaytreatment/

Heinrich N, Wubker A, Wuckel C. Waiting Times for Outpatient Treatment in Germany: New Experimental Evidence from Primary Data. Journal of Economics and Statistics. 2018;238(5):375-394.

Holt MR, Hand MM. The pharmacist's role in reducing patient delay in seeking treatment for acute myocardial infarction. Journal of the American Pharmacists Association. 1999;39(6):752-757.

Huang C, Iqbal U, Li Y, Healthcare improvement measures in risk management and patient satisfaction. International Journal for Quality in Health Care. 2018;30(1):1.

Kandukuri RC, Khan MA, Soltys SM. Nonadherence to medication in hypothyroidism: a case report. The Primary Care Companion to the Journal of Clinical Psychiatry [Internet] 2010 [cited 2021 May 14] ;12(3):PCC.09m00863. Available from URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2947542/

Kinoshita Y, Ishimura N, Ishihara S. Advantages and Disadvantages of Long-term Proton Pump Inhibitor Use. Journal of Neurogastroenterology and Motility. 2018;24(2):182-196.

Kraft AD, Quimbo S, Solon O, Shimkhada R, Florentino J, Peabody JW. The Health and Cost Impact of Care Delay and the Experimental Impact of Insurance on Reducing Delays. The Journal of Pediatrics [Internet] 2009 [cited 2021 May 14] ;155(2):281-285. Available from URL: https://www.jpeds.com/article/S0022-3476(09)00156-5/pdf,

Kompelli AR, Li H, Neskey DM. Impact of delay in treatment initiation on overall survival in laryngeal cancers. JAMA Otorhinolaryngology – Head & Neck Surgery. 2019;160(4):651-657.

Kubica A, Obońska K, Kasprzak M, Sztuba B, Navarese EP, Koziński M, et al. Prediction of high risk of non-adherence to antiplatelet treatment. Kardiologia Polska. 2016;74(1):61-67.

Lago P, Bizzarri G, Scalzotto F, Parpaiola A, Amigoni A, Putoto G, et al. Use of FMEA analysis to reduce risk of errors in prescribing and administering drugs in paediatric wards: A quality improvement report. BMJ Open [Internet] 2012 [cited 2021 May 14] ;2:e001249. Available from URL: https://bmjopen.bmj.com/content/2/6/e001249

Luu NM, Dinh AT, Nguyen TTH, Nguyen VH. Adherence to Antiplatelet Therapy after Coronary Intervention among Patients with Myocardial Infarction Attending Vietnam National Heart Institute. BioMed Research International [Internet] 2019 [cited 2021 May 14] ;ID6585040. Available from URL: https://www.hindawi.com/journals/bmri/2019/6585040/

Mahmood Z, McNamara D. Gastro-oesophageal reflux disease and ulcer disease. Alimentary Pharmacology and Therapeutics. 2003;18(3):31-37.

Mandelzweig L, Goldbourt U, Boyko V, Tanne D. Perceptual, Social, and Behavioral Factors Associated With Delays in Seeking Medical Care in Patients With Symptoms of Acute Stroke. Stroke. 2006;37(5):1248-1253.

Maringe C, Spicer J, Morris M, Puroshotham A, Nolte E, Sullivan R, Rachet B, Aggarwal A. The impact of the COVID-19 pandemic on cancer deaths due to delays in diagnosis in England, UK: a national, population-based, modelling study. The Lancet Oncology [Internet] 2020 [cited 2021 May 14] ;21:1023–34. Available from URL: https://www.thelancet.com/action/showPdf?pii=S1470-2045%2820%2930388-0

Martin D, Miller AP, Quesnel-Vallée A, Caron NR, Vissandjée B, Marchildon GP. Canada's universal health-care system: achieving its potential. Lancet. 2018;391(10131):1718–35.

Mauri L, Elmariah S, Yeh RW, Cutlip DE, Steg PG, Windecker S, et al. Causes of late mortality with dual antiplatelet therapy after coronary stents. European Heart Journal. 2016;37(4):38-385.

Mellish L, Karanges EA, Litchfield MJ, Schaffer AL, Blanch B, Daniels BJ, et al. The Australian Pharmaceutical Benefits Scheme data collection: a practical guide for researchers. BMC Research Notes [Internet] 2015 [cited 2021 May 14] ;8:634. Available from URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4630883/#CR17

Mhalu G, Weiss MG, Hella J. Mhimbira F, Mahongo E, Shindler C, et al. Explaining patient delay in healthcare seeking and loss to diagnostic follow-up among patients with presumptive tuberculosis in Tanzania: a mixed-methods study. BMC Health Services Research [Internet] 2019 [cited 2021 May 14] ;19, 217. Available from URL: https://bmchealthservres.biomedcentral.com/articles/10.1186/s12913-019-4030-4

Moser D, Kimble LP, Alberts MJ, Alonzo A, Croft JB, Dracup K. Reducing Delay in Seeking Treatment by Patients With Acute Coronary Syndrome and Stroke: A Scientific Statement From the American Heart Association Council on Cardiovascular Nursing and Stroke Council. Circulation. 2006;114(2):168.182.

Nolan DP. Handbook of Fire and Explosion Protection Engineering Principles. Elsevier Inc. 2011:113-118.

O'Neill LW, Culpepper BL, Galdo JA. Long-Term Consequences of Chronic Proton Pump Inhibitor Use. Gastroenterology. 2013;38(12):38-42.

Pace F, Annese V, Prada A, Zambelli A, Casalini S, Nardini P, Bianchi Porro G; Italian Rabeprazole Study Group. Rabeprazole is equivalent to omeprazole in the treatment of erosive gastro-oesophageal reflux disease. A randomised, double-blind, comparative study of rabeprazole and omeprazole 20 mg in acute treatment of reflux oesophagitis, followed by a maintenance open-label, low-dose therapy with rabeprazole. Digestive and Liver Disease. 2005;37(10):741-750.

Pandé R, Hodson J, Murray A, Marcon F, Kalisvaart M, Marudanayagam R, et al. Evaluation of the clinical and economic impact of delays to surgery in patients with periampullary cancer. British Journal of Surgery Society Ltd. [Internet] 2019 [cited 2021 May 14] ;3(4):476-484. Available from URL: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6677092/

Park SJ, Sharp AL. Improving health and health care efficiency through risk management. Journal of Hospital Management and Health Policy. 2019;3:9.

Penttilä M, Jääskeläinen E, Hirvonen N, Isohanni M, Miettunen J. Duration of untreated psychosis as predictor of long-term outcome in schizophrenia: systematic review and meta-analysis. British Journal of Psychiatry. 2014;205(2):88-94.

Prentice JC, Pizer SD. Delayed access to health care and mortality. Health Services Research. 2007;42(2):644-662.

Ratna H. The Importance of Effective Communication in Healthcare Practice. Harvard Public Health Review. 2019:23.

Reichert A, Jacobs R. The impact of waiting time on patient outcomes: Evidence from early intervention in psychosis services in England. Health Economics. 2018;27(11):1772-1787.

Reisinger MW, Moss M, Clark BJ. Is lack of social support associated with a delay in seeking medical care? A cross-sectional study of Minnesota and Tennessee residents using data from the Behavioral Risk Factor Surveillance System. BMJ Open [Internet] 2018 [cited 2021 May 14] ;8:e018139. Available from URL: https://bmjopen.bmj.com/content/8/7/e018139.citation-tools

Richard P, Walker R, Alexandre P. The burden of out of pocket costs and medical debt faced by households with chronic health conditions in the United States. PLoS ONE [Internet] 2018 [cited 2021 May 14] ;13(6): e0199598. Available from URL: https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0199598#pone.0199598.ref007

Rivero F, Bastante T, Cuesta J, Benedicto A, Salamanca J, Restrepo J, et al. Factors Associated With Delays in Seeking Medical Attention in Patients With ST-segment Elevation Acute Coronary Syndrome. Revista Espanola de Cardiologia [Internet] 2016 [cited 2021 May 14] ;69(3):279-285. Available from URL: https://www.revespcardiol.org/en-factors-associated-with-delays-in-articulo-S1885585715003667

Sarkar M, Hennessy S, Yang YX. Proton-pump inhibitor use and the risk for community-acquired pneumonia. Annals of Internal Medicine. 2008;149:391-398.

Shimura S, Hamamoto N, Yoshino N, Kushiyama Y, Fujishiro H, Komazawa Y, et al. Diarrhea caused by proton pump inhibitor administration: comparisons among lansoprazole, rabeprazole, and omeprazole. Current Therapeutic Research: Clinical and Experiential. 2012;73(3):112-120.

Soekhlal RR, Burgers LT, Redekop WK, Tan SS. Treatment costs of acute myocardial infarction in the Netherlands. Netherlands Heart Journal. 2013;21(5):230-235.

Sweiss K, Wirth SM, Sharp L, Park I, Sweiss H, Rondelli D, et al. Collaborative Physician-Pharmacist–Managed Multiple Myeloma Clinic Improves Guideline Adherence and Prevents Treatment Delays. Journal of Oncology Practice [Internet] 2018 [cited 2021 May 14] ;14(11):674-682. Available from URL: https://ascopubs.org/doi/full/10.1200/JOP.18.00085

Tang N, Eisenberg JM, Meyer GS. The roles of government in improving health care quality and safety. Joint Commission Journal on Quality and Safety. 2004;30(1):47-55.

Taghaddosi M, Dianati M, Fath Gharib Bidgoli J, Bahonaran J. Delay and its related factors in seeking treatment in patients with acute myocardial infarction. ARYA Atherosclerosis. 2010;6(1):35-41.

Victoor A, Friele RD, Delnoij DM, Rademakers JJ. Free choice of healthcare providers in the Netherlands is both a goal in itself and a precondition: modelling the policy assumptions underlying the promotion of patient choice through documentary analysis and interviews. BMC Health Service Research. 2012;12:441.

Walter F, Webster A, Scott S, Emery J. The Andersen Model of Total Patient Delay: a systematic review of its application in cancer diagnosis. Journal of Health Services Research & Policy. 2012;17(2):110-118.

Wang PS, Angermeyer M, Borges G, Bruffaerts R, Chiu WT, De Girolamo G, et al. Delay and failure in treatment seeking after first onset of mental disorders in the World Health Organization's World Mental Health Survey Initiative. World Psychiatry. 2007;6(3):177-185.

Wang YF, Chen YT, Luo JC, Chen TJ, Wu JC, Wang SJ. Proton-Pump Inhibitor Use and the Risk of First-Time Ischemic Stroke in the General Population: A Nationwide Population-Based Study. The American Journal of Gastroenterology. 2017;112(7):1084-1093.

Weissman JS, Stern R, Fielding SL, Epstein AM. Delayed access to health care: risk factors, reasons, and consequences. Annals of Internal Medicine. 1991;114(4):325-331.

Xie Y, Bowe B, Li T, Xian H, Yan Y, Al-Aly Z. Risk of death among users of Proton Pump Inhibitors: a longitudinal observational cohort study of United States veterans. BMJ Open [Internet] 2017 [cited 2021 May 14] ;7(6):e015735. Available from URL: https://bmjopen.bmj.com/content/7/6/e015735.long

Appendices

Appendix 1

Schedule V Conditions and Forms for POYC Medicines Approval System

List of chronic conditions included in Schedule V

1. Malignant Diseases

2. Cardiovascular Diseases:
    a) Chronic Heart Failure
    b) Hypertension
    c) Ischaemic Heart Disease
    d) Cardiac Arrhythmias
    e) Peripheral Vascular Disease
    f) Cerebrovascular disease
    g) Genetic Dyslipidaemia

3. Respiratory Diseases:
    a) Chronic Respiratory Failure
    b) Cystic Fibrosis
    c) Chronic Obstructive Pulmonary Disease
    d) Chronic Asthma

4. Digestive System Diseases:
    a) Gastro – Oesophageal Reflux Disease
    b) Gastric/Duodenal Ulcers
    c) Inflammatory Bowel Disease
    d) Coeliac Disease

e) Diverticular Disease requiring Stoma Care

f) Hirschprung's Disease

g) Imperforate Anus

h) Small Intestinal Failure

5. Liver Diseases: Chronic Liver Disease

6. Haematological Diseases:

    a) Inherited Bleeding Disorders

    b) Inherited Haemoglobinopathies

7. Nervous System Diseases:

    a) Epilepsy

    b) Parkinson's Disease

    c) Myasthenia Gravis

    d) Multiple Sclerosis

    e) Motor Neurone Disease

    f) Trigeminal Neuralgia

    g) Huntington's Chorea

    h) Dementia

    i) Schizophrenia

    j) Psychosis

    k) Chronic Mood Disorders

    l) Chronic Neurotic Disorders

m) Addiction Disorders

n) Chronic Psychiatric Disorders starting in Childhood

o) Chronic Eating Disorders

p) Cerebral Palsy

q) Narcolepsy

r) Spinal Cord Pathologies

s) Congenital Indifference to pain

8. Renal Diseases: Chronic Kidney Disease

9. Endocrine Diseases:

    a) Diabetes Mellitus

    b) Addison's Disease

    c) Precocious Puberty

    d) Hypoparathyroidism

    e) Hypopituitarism

    f) Hypogonadism

    g) Enzyme Disorders

    h) Endometriosis and Adenomyosis

    i) Pituitary Adenomas

10. Skin Diseases:

    a) Psoriasis

    b) Chronic Immunobullous Disorders

c) Congenital Ichthyosis

11. Infectious Diseases:

a) HIV/AIDS and HIV Related Diseases

b) Hepatitis B & C

c) Tuberculosis

d) Hospital Acquired Infections

e) Leprosy

f) Polio and Post-Polio Syndrome

g) Chronic Osteomyelitis

12. Rheumatic Diseases:

a) Rheumatoid Arthritis

b) Paget's Disease

c) Lupus Erythematosus

d) Systemic Sclerosis

e) Dermatomyositis/Polymyositis

f) Polyartritis Nodosa

g) Seronegative Arthritis

h) Crystal Deposition Disease

i) Polymyalgia Rheumatica

13. Metabolic Disorders: Inborn Errors of Metabolism

14. Eye Diseases:

    a) Glaucoma

    b) Vascular Disease of the Retina

15. Immunodeficiency:

    a) Primary Immunodeficiency Disorder

    b) Secondary Immunodeficiency Disorder

16. Chromosome Disorders:

    a) Down Syndrome

    b) Turner Syndrome

    c) Prader-Willi Syndrome

Pharmacy of Your Choice Forms

POYC
PHARMACY OF YOUR CHOICE

Medicines Approval Section

Reset form

Pharmacy Of Your Choice Unit
St. Luke's Square, G'Mangia
email: scheduler.poyc@gov.mt
tel.no. 21233424 / 22481800

Request Form for the supply of Free Drugs in terms of Schedule V (Part II) of Social Security Act (2012)

Patient Name		Date of Birth	
Address			
ID. Card No.		Telephone No.	

Please tick ☑ Schedule V condition accordingly:

- ☐ Addiction Disorders
- ☐ Addison's Disease
- ☐ Benign Prostatic Enlargement
- ☐ Cardiac Arrhythmias
- ☐ Cerebral Palsy
- ☐ Cerebrovascular disease
- ☐ Chronic Asthma
- ☐ Chronic Eating Disorders
- ☐ Chronic Heart Failure
- ☐ Chronic Immunobullous Disorders
- ☐ Chronic Kidney Disease
- ☐ Chronic Liver Disease
- ☐ Chronic Mood Disorders
- ☐ Chronic Neurotic Disorders
- ☐ Chronic Obstructive Pulm. Disease
- ☐ Chronic Osteomyelitis
- ☐ Chronic Psychiatric Disorders starting in Childhood
- ☐ Chronic Respiratory Failure
- ☐ Coeliac Disease
- ☐ Congenital Ichthyosis
- ☐ Congenital indifference to pain
- ☐ Crystal Deposition Disease
- ☐ Cystic Fibrosis
- ☐ Dementia
- ☐ Type 1 Diabetes
- ☐ Other Types of Diabetes
- ☐ Gestational Diabetes
- ☐ Dermatomyositis/Polymyositis
- ☐ Diverticular Disease requiring Stoma Care
- ☐ Down Syndrome
- ☐ Endometriosis and Adenomyosis
- ☐ Enzyme Disorders
- ☐ Epilepsy
- ☐ Fibromyalgia
- ☐ Gastric/Duodenal Ulcers
- ☐ Gastro-Oesophageal Reflux Disease
- ☐ Gender Identity & Sex Characteristics Related Conditions
- ☐ Genetic Dyslipidaemia
- ☐ Glaucoma
- ☐ Hepatitis B & C
- ☐ Hirschsprung's Disease
- ☐ HIV/AIDS and HIV Related Diseases
- ☐ Hospital Acquired Infections
- ☐ Huntington's Chorea
- ☐ Hypertension
- ☐ Hypogonadism
- ☐ Hypoparathyroidism
- ☐ Hypopituitarism
- ☐ Imperforate Anus
- ☐ Inborn errors of Metabolism
- ☐ Inflammatory Bowel Disease
- ☐ Inherited Bleeding Disorders
- ☐ Ischaemic Heart Disease
- ☐ Inherited Haemoglobinopathies
- ☐ Leprosy
- ☐ Lupus Erythematosus
- ☐ Malignant Diseases
- ☐ Motor Neurone Disease
- ☐ Multiple Sclerosis
- ☐ Myasthenia Gravis
- ☐ Myalgic Encephalomyelitis
- ☐ Narcolepsy
- ☐ Neuromyelitis Optica
- ☐ Paget's Disease
- ☐ Parkinson's disease
- ☐ Peripheral Vascular Disease
- ☐ Pituitary Adenomas
- ☐ Polio and Post-Polio
- ☐ Polyarteritis Nodosa
- ☐ Polymyalgia Rheumatica
- ☐ Prader-Willi Syndrome
- ☐ Precocious Puberty
- ☐ Primary Immunodeficiency Disorder
- ☐ Psoriasis
- ☐ Psychosis
- ☐ Rheumatoid Arthritis
- ☐ Schizophrenia
- ☐ Secondary Immunodeficiency Disorder
- ☐ Small Intestinal Failure
- ☐ Spinal Cord Pathologies
- ☐ Spondyloarthritis
- ☐ Systemic Sclerosis
- ☐ Trigeminal Neuralgia
- ☐ Tuberculosis
- ☐ Turner Syndrome
- ☐ Vascular Disease of the Retina

☐ By marking this box, I am accepting that previously approved treatment may be added to the patient's entitlement document.

i. PLEASE NOTE that in line with current Policy Direction in order to enable a patient to access his / her medication, the following documentation must be attached to this Form:

a. The current Schedule V Card

b. The following additional documentation [as appropriate]:

Atorvastatin and Rosuvastatin	☐ LDL report
Clopidogrel	☐ Stent report and / or Admission dates
Donepezil	☐ Form D1
Gluten-free diet	☐ Duodenal biopsy report
Repaglinide	☐ eGFR blood test and/or BMI [Height: _____ m, Weight: _____ kg, BMI: _____ kg/m²] and/or post-prandial hyperglycaemia
Gliptins	AND ☐ Part A: HbA1c blood test OR ☐ Part B: Intolerance to Metformin ☐ HbA1c blood test

HbA1c results may not be older than 4 months

Data Protection Statement: The Ministry for Health shall be responsible for the information compiled in this form. Every individual reserves the right to request in writing, to see all the information compiled on him/her. This information shall be used solely for the purpose of issuing medicines entitlement to beneficiaries in terms of the Schedule V legislation.

Patient Name		ID. Card No.	

Drug & Dosage Form Requested:		Protocol Number (Where applicable)	Strength: (POYC records ONLY)	Dosage Regimen: (POYC records ONLY)
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				

RENEWAL OF PROTOCOL REGULATED MEDICINE	
Drug & Dosage Form Requested:	
1.	
2.	
3.	
4.	
5.	

I hereby certify that this treatment for free medicine entitlement is being requested according to the stated condition covered by the provisions of Schedule V (Part II) of the Social Security Act and that all details provided are true and correct. I confirm that I have read the specific protocol/s, and the clinical conditions and specific terms set by the specific protocol/s have been met.

Applicant's Signature

Applicant's Name (in block letters)

Medical Registration No.

Date

Rubber Stamp

Email form

ii. Please Note:

a. Only Forms endorsed by the Government Consultants and designated Medical Practitioners will be recognized.

b. An *Acknowledgement* will be sent to the prescriber upon receipt of the Application.

c. In case of a RENEWAL of an expired Card, PERMIT or CHANGE in TREATMENT, the Sch V Card that needs to be amended must be attached to this Application.

d. Any queries or requests should be addressed to the POYC Unit on email schedulev.poyc@gov.mt.

POYC
PHARMACY OF YOUR CHOICE

Pharmacy Of Your Choice Unit
St Luke's Hospital, G'Mangia
Email: schedulev.poyc@gov.mt

Tel. No. 21232424 / 22481800
Gozo Branch Tel. No. 22156448

DATE _____

YOUR REF _____

OUR REF _____

Sir/Madam,

You are kindly requested to call at this office during working days (Monday to Friday) from 08.00 to 13.00.

a) If you are working in Malta and paying N.I. Contributions, please bring with you last month's pay slip. If you are self-employed you are requested to present the most recent (not older than 6 months) receipt of N.I. contributions.

b) If you are married to a Maltese citizen, please bring a photocopy of your spouse's I.D. Card and a photocopy of the marriage certificate.

c) If you are in receipt of a Maltese state pension, you are requested to present the notice of pension payment (not older than 6 months) issued by Social Security Department.

d) If you are an EU citizen residing in Malta on a permanent basis, you are requested to present a Certificate of Entitlement issued by the Entitlement Unit within the Ministry for Health, as well as proof of identity. Kindly note that the Entitlement Unit may only issue a Certificate of Entitlement upon presentation of any of the following forms: E106, E109 and E121 or form S1. These forms are issued by the competent authorities of your country of origin, if you are in receipt of a state pension from that country or you are working in Malta and paying social contributions in your country of origin.

e) If you are a refugee kindly present your refugee certificate.

f) If you are an asylum seeker or have subsidiary protection status, kindly present your certificate indicating such status.

g) If you (or your dependents) are an EU/EAA national and have permanent residence status, kindly present your ID (Residence) card.

h) Should you need further clarification about your healthcare entitlement status you may contact the Entitlement Unit by email: entitlement.health@gov.mt or by phoning on: 25952400.

In case of any difficulty please phone the **POYC Medicines Approval Section** on Tel No: 21232424 / 22481800 on the days and times indicated above.

Directorate for Pharmaceutical Affairs
Ministry for Health
Administration Building, St. Luke's Hospital, G'Mangia
Email: dpa.health@gov.mt Tel. No: 2595 5232

Exceptional Medicinal Treatment Request Form

Patient's Name

Date of Birth | **I.D. Card Number** | **Mobile Number**

Address

Request ☐ First Application ☐ Renewal

Entitlement to Free Medicines
☐ Schedule V Condition
☐ Schedule II
☐ No Schedule II or Schedule V entitlement

Medication Requested | **Dosage Form and Strength**

Dosage Regimen | **Expected Duration of Therapy**

Clinical Indications

Reason/s why this drug is requested

Further documentation needed: Laboratory results etc

Signature of Consultant | **Signature of Clinical Chairperson**

Name in BLOCK LETTERS and Registration Number | **Name in BLOCK LETTERS and Registration Number**

Date: | **Date:**

For Office Use only: ☐ *Approved* ☐ *Not Approved* *Date:*

This form will be returned to the Consultant if any section is not completed

Data Protection Statement
All personal data is required to provide you with health care services as necessary, and is processed in accordance with the Data Protection Act, and as permitted by law. Further information about your data can be obtained on request

POYC
PHARMACY OF YOUR CHOICE

Pharmacy Of Your Choice Unit
St Luke's Hospital, G'Mangia
Email: scheduler.poyc@gov.mt

Tel. No. 21 232424 / 22481800
Gozo Branch Tel. No. 22156448

Referenza *Reference*	Data *Date*

Għażiż Sinjur/a,

Dear Sir/Madam,

Nixtieq ninfurmak li l-applikazzjoni tal-Kartuna s-Safra ma ġietx approvata għall-mediċini msemmija, minħabba li:

I would like to inform you that your Yellow Card application was not approved for the following medicines because:

	Dawn il-mediċini mhumiex fil-Lista tal-Formularju tal-Gvern. https://ehealth.gov.mt/download.aspx?id=9365	*These medicines are not in the Government Formulary List.* https://ehealth.gov.mt/download.aspx?id=9365
	L-applikazzjoni għall-Kartuna Safra mhix skont il-*policies* tad-Direttorat li taħtu jaqa' dan l-uffiċċju.	*This application for the Yellow Card is not according to policies stipulated by this Directorate.*
	Din il-marda / kundizzjoni mhix waħda minn dawk li għalihom jingħataw mediċini bla ħlas. https://ehealth.gov.mt/download.aspx?id=2395	*This disease / condition is not one of those for which free medicines are given.* https://ehealth.gov.mt/download.aspx?id=2395
	Jekk jogħġbok kellem lill-Konsulent biex tapplika għall-permess / Kartuna s-safra.	*Kindly talk to the Consultant to apply for a permit / Schedule V.*
	Dawn il-mediċini ma jiġux approvati għall-mard / kundizzjonijiet immarkati fl-applikazzjoni għall-Kartuna Safra. https://ehealth.gov.mt/download.aspx?id=9364	*These medicines are not approved for diseases / conditions ticked in the application for the Yellow Card.* https://ehealth.gov.mt/download.aspx?id=9364

Grazzi,
Thank you,

_____
Uffiċjal MAS

Appendix 2

Ethics Approval by Faculty of Medicine and Surgery Research Ethics Committee

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: FREC\MDS_2021_035

Thursday 7 January 2021

Mr Charles Mandy Ayran
Flat 28, Little Gozo Court
Triq G Calleja,
Swatar
Msida MSD2270

Dear Mr Ayran,

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

A Review of the POYC Medicines Approval System

The Faculty Research Ethics Committee granted ethical approval for the above mentioned application which was reviewed on 22 December 2020.

Yours sincerely,

Professor Pierre Mallia
Chairman
Faculty Research Ethics Committee

Appendix 3

Interview Guide and Information for Key Informants in Phase 3

A REVIEW OF THE POYC MEDICINES APPROVAL SYSTEM

INFORMATION FOR KEY INFORMANTS

(Phase 3: Development of Pharmacist Interventions)

Aim of the Study:

To optimise the POYC Medicines Approval System through pharmacist interventions to promote an efficient service delivery to patients

Objective of Phase 3:

To develop pharmacist interventions targeted to streamline access to approval of entitlements

Duration of Interview:

1 to 1.5 hours

Interview Guide:

1. Brief presentation of Phase 1 (risk identification) and Phase 2 (risk assessment and prioritisation using FMEA) results

2. Development of pharmacist interventions for implementation

    2.1. Based on the interventions partially identified by a panel from Phase 2, which of the interventions could be adapted by POYC for implementation? The following are the

interventions identified by the panel to mitigate potential failure modes that are of critical risks:

2.1.1. Development of an orientation manual/handbook for prescribers and pharmacists

2.1.1.1. What are the specific contents of the manual that will allow prescribers and pharmacists to be familiarized with the approval system?

2.1.1.2. How should the manual be rolled-out to ensure maximum coverage among prescribers and pharmacists?

2.1.2. Extensive and pro-active roll-out of online applications via CARE among authorized prescribers

2.1.2.1. What are the POYC client support strategies currently in place for authorized prescribers, who are current CARE users?

2.1.2.2. What strategies should be adapted by POYC to encourage authorized prescribers to use CARE when applying for Schedule V?

2.1.2.3. How would POYC-MAS handle an influx of online CARE applications?

2.1.3. Implementation of feedback system between POYC, DPA, prescribers, and pharmacists on non-approval data

2.1.3.1. How could POYC transform available data on non-approvals into a valuable feedback to DPA, prescribers, and pharmacists?

2.1.3.2. How regular should POYC provide feedback to DPA, prescribers, and pharmacists?

2.1.3.3. What medium is recommended for prescribers and pharmacists who would want to provide feedback regarding the approval system?

2.1.4. Regular formulary and protocol review

2.1.4.1. What is the extent of involvement of POYC in the formulary and protocol review being done by DPA?

2.1.5. Linking of POYC and other government databases

2.1.5.1. How can POYC gain access to other government databases/records necessary for the approval of Schedule V applications (i.e. National Insurance contribution, Certificates of Entitlement, Refugee Certificates, Case Summaries and Test Results)

2.1.5.2. Are there data protection and privacy issues , or lack of IT support, which prevent such set-up?

2.2. Are there other additional interventions, not yet identified, that could be vital in mitigating risks associated with non-approvals that are of preventable causes?

2.3. Who are the specific section/s or person/s responsible in carrying out these interventions?

2.4. What are the outcome measures that can be used to determine success of the interventions to be implemented?

- END OF INTERVIEW/MEETING -

Appendix 4

Steps in the POYC Medicines Approval System and the Potential Failure Modes

Procedure	Potential Failure Modes
1. Patient consults an authorised prescriber	1.1 Prescriber did not apply for Schedule V
2. Authorised prescriber fills out Schedule V application form	2.1 Prescriber used the wrong form 2.2 Prescriber did not apply for permit nor write protocol number for application of permit for protocol-regulated medicines 2.3 Prescriber did not sign application form 2.4 Prescriber's signature not recognisable nor legible 2.5 Prescriber not eligible to apply for Schedule V or permit 2.6 Prescriber did not complete patient information (for example, name, ID number, address, date of birth) for access and confirmation 2.7 Prescriber wrote the wrong patient information (for example, name and ID number not matching, C number for babies) 2.8 Prescriber applied for non-protocol regulated medicines in Schedule V for patients who are not eligible in the scheme (for example, Asylum Seekers, Subsidiary Protection)

Procedure	Potential Failure Modes
3. Patient submits the Schedule V application form and/or supporting documents to POYC – Medicines Approval Section (MAS) for evaluation	3.1 Patient failed to bring original application form (photocopies not accepted) 3.2 Patient submitted ticket of referrals or prescriptions instead of the application form 3.3 Foreign patient failed to bring supporting documents (for example, payslip, certificate of entitlement [COE], pension slip) to confirm eligibility in the scheme 3.4 Patient did not present at POYC-MDH on the same day as the application
4. POYC-MAS Officer evaluates and approves application based on the outpatients GFL and protocol for certain medications	4.1 Medicine is not on the GFL 4.2 Medicine is for in-patient use only 4.3 Wrong prescriber criteria 4.4 Medicine did not correspond to Schedule V condition 4.5 Prescriber applied for a condition that is not considered under Schedule V 4.6 Prescriber did not tick or indicate Schedule V condition or diagnosis in the application form 4.7 Application was not according to protocol 4.8 Application did not have the supporting document (for example, low-density lipoprotein

Procedure	Potential Failure Modes
	[LDL] report, glycated haemoglobin [HbA1c] test, control card) as required by the protocol 4.9 Patients who benefit from Schedule II (pink card) for diabetes treatment must renounce Schedule II before registering for Schedule V for diabetes mellitus medications 4.10 Application was awaiting approval from the DPA for exceptional cases 4.11 Medicine was not specified (for example, angiotensin-converting enzyme inhibitor [ACEI] instead of specifying Enalapril, Perindopril, or Lisinopril) 4.12 Medicine listed not legible

Appendix 5

Case Descriptions for the POYC-MAS Potential Failure Modes

Potential Failure Modes	Case Descriptions
1.1 Prescriber did not apply for Schedule V	Patients could go to POYC-MAS under the impression that the prescriber have already applied for Schedule V (online through CARE or actual application sent by post to POYC), when in reality, the application has not been done yet.
2.1 Prescriber used the wrong form	Prescriber used the protocol-regulated form for non-protocol-regulated medicines. Prescriber used old forms no longer acceptable by POYC-MAS or DPA.
2.2 Prescriber did not apply for permit for protocol-regulated medicines (no protocol number in Schedule V application form, or no protocol-regulated form filled out)	Prescriber did not indicate the protocol number (for example, #276 for Clopidogrel) of the protocol-regulated medicine in the Schedule V application form, in addition, no protocol-regulated form was attached.
2.3 Prescriber did not sign application form	Prescriber forgot to sign the application form. Prescriber wrote their name or registration number only, and without signature.
2.4 Prescriber's signature and other credentials not recognisable nor legible	Prescriber completed the signature part of the application form, but in an illegible manner.

Potential Failure Modes	Case Descriptions
2.5 Prescriber not eligible to apply for Schedule V or permit	Prescriber is not a registered health center doctor. Prescriber is not a registered delegate of an eligible MDH consultant.
2.6 Prescriber did not complete patient information (for example, name, ID number, address, date of birth) for access and confirmation	POYC-MAS needs to at least verify both name and ID number of patient to access their profile in CARE. Schedule V document may be posted to the wrong or old address.
2.7 Prescriber wrote the wrong patient information (for example, name and ID number not matching, C number for babies, F number for foreigners)	POYC-MAS requires registered Maltese ID card numbers (those not ending in C or F) to access patient profile in CARE. For foreigners awaiting ID cards, a temporary handwritten Schedule V valid for 3 months is issued only upon confirmation that patient still does not have an ID card.
2.8 Prescriber applied for non-protocol regulated medicines in Schedule V for patients who are not eligible in the scheme (for example, Asylum Seekers, Subsidiary Protection)	Patients considered as asylum seekers, under subsidiary protection, or Corradino Correctional Facility (CCF) inmates are not eligible for Schedule V. POYC-MAS only issues a handwritten permit for protocol-regulated medicines, but not for non-protocol-regulated medicines.
3.1 Patient failed to bring original application form (photocopies not accepted)	POYC-MAS only accepts original application forms to prevent patients from recycling

Potential Failure Modes	Case Descriptions
	photocopies of application forms in the succeeding renewals of Schedule V.
3.2 Patient submitted ticket of referrals or prescriptions instead of the application form	Patients could mistakenly go to POYC-MAS under the impression that ticket of referrals or prescriptions are valid documents for Schedule V application.
3.3 Foreign patient failed to bring supporting documents (for example, payslip, COE, pension slip) to confirm eligibility in the scheme	Foreign patients are required to show proof of their eligibility in the scheme before processing their application. They are usually asked for their COE, national insurance contribution as per payslips, marriage certificate if married to a Maltese citizen, or refugee certicate.
3.4 Patient did not present at POYC-MDH on the same day as the application	POYC-MDH only caters to applications signed by prescribers on the same day as to when the patient would go to POYC-MDH. Otherwise, patients are directed to POYC-SLH or POYC-Paola.
4.1 Medicine is not on the GFL	Prescriber applied for a medicine that is not currently on the government formulary list (for example, nitroglycerin spray, aripiprazole)
4.2 Medicine is for in-patient use only	Prescriber applied for a medicine that is in the government formulary list, but is considered for in-

Potential Failure Modes	Case Descriptions
	patient use only (for example, Fulvestrant Protocol #79).
4.3 Wrong prescriber criteria	Prescriber did not meet the prescriber criteria required by the government formulary list or protocol (for example, only consultant oncologists may apply for Abiraterone as per Protocol #8 -- this means that prescribers from other specializations are not eligible to apply for this medicine).
4.4 Medicine did not correspond to Schedule V condition	Prescriber applied for a medicine under a Schedule V condition for which it is not mapped as per the government formulary list (for example, Oral Rehydration Powder is only mapped under Malignant Disease -- this means that the medicine would not be approved if it is applied for under Hypertension).
4.5 Prescriber applied for a condition that is not considered under Schedule V	Prescriber applied for a medicine under a condition that is not considered under Schedule V (for example, Hyperthyroidism)
4.6 Prescriber did not tick or indicate Schedule V condition or diagnosis in the application form	Prescriber did not fill out the first page of the Schedule V application form.

Potential Failure Modes	Case Descriptions
4.7 Application was not according to protocol	Prescriber submitted the requirements to apply for a protocol-regulated medicine but evaluated as not according to the set protocol (for example, Vildagliptin as per Protocol #89 states that it is reserved for patients with an HbA1c >7% and <10% despite treatment with sulphonylurea or Repaglinide -- this means that if the HbA1c test result attached is 6.9%, the application would not be approved).
4.8 Application did not have the supporting document (for example, lipid profile, HbA1c test, control card) as required by the protocol	Patient submitted the Schedule V and permit application but not the required supporting document as required by protocol (for example, LDL report for Rosuvastatin, stent report or case summary for Clopidogrel, form D1 showing Mini-mental State Examination [MMSE] score for Donepezil, duodenal biopsy report for gluten-free diet vouchers for Coeliac patients, HbA1c report for Vildagliptin, Atomoxetine request form for Atomoxetine, Omalizumab request form for Omalizumab, control card for Methylphenidate prolonged-release tablets and Atomoxetine).

Potential Failure Modes	Case Descriptions
4.9 Patients who benefit from Schedule II (pink card) for diabetes treatment must renounce Schedule II before registering for Schedule V for diabetes mellitus medications	Patients who are considered as disease-associated individuals under Schedule II must renounce their Schedule II first before being eligible for Schedule V for diabetes mellitus medications.
4.10 Application was awaiting approval from the DPA for exceptional cases	DPA is the body in-charge of approving exceptional medicine treatment requests. Approved medicines for exceptional cases that are to be added in the Schedule V are communicated to POYC-MAS by DPA through a confirmatory email.
4.11 Medicine was not specified (for example, ACEI instead of specifying Enalapril, Perindopril, or Lisinopril)	Prescriber applied for a drug class instead of a specific medicine (for example, ACEI instead of specifying if it is Enalapril, Perindopril, or Lisinopril; oral steroids instead of specifying if it is Hydrocortisone, Dexamethasone, or Prednisolone).
4.12 Medicine listed not legible	Prescriber applied for medicine but handwriting cannot be recognised nor read.

Appendix 6

Grading Scales for Severity, Occurrence, and Detectability in FMEA

Grading scale for Severity in FMEA

Grade	Description
1	**None:** does not cause delay in treatment
2	**Minor:** may cause delay in treatment that is less than 24 hours
3	**Moderate:** may cause delay in treatment that is more than 24 hours but less than seven (7) days
4	**High:** may cause delay in treatment that is more than seven (7) days but less than one (1) month
5	**Serious:** may cause delay in treatment that is more than one (1) month
***Severity:** the degree to which the potential failure mode may cause delay in treatment as measured using the above ordinal scale	

Grading scale for Occurrence in FMEA

Grade	Description
1	**Almost never:** contributed to **less than 0.01 per hundred** (<1 in 10,000) of the process-specific reasons per year for the added partial and full non-approvals
2	**Minor:** contributed to **greater than or equal to 0.01 per hundred** (>=1 in 10,000) **but less than 0.1 per hundred** (<1 in 1000) of the process-specific reasons per year for the added partial or full non-approvals
3	**Moderate:** contributed to **greater than or equal to 0.1 per hundred** (>=1 in 1000) **but less than 1 per hundred** (<1 in 100) of the process-specific reasons per year for the added partial or full non-approvals
4	**High:** contributed to **greater than or equal to 1 per hundred** (>=1 in 100) **but less than 2 per hundred** (<1 in 50) of the process-specific reasons per year for the added partial or full non-approvals
5	**Very high:** contributed to **greater than or equal to 2 per hundred** (>= 1 in 50) of the process-specific reasons per year for the added partial or full non-approvals
***Occurrence:** the degree to which the potential failure mode may happen as measured using the above ordinal scale based on Phase 1 results	

Grading scale for Detectability in FMEA

Grade	Description
1	**First-contact:** may be observed or recognised by patient/relative prior to Schedule V application
2	**Second-contact:** may be observed or recognised by applying doctor while preparing the Schedule V application form
3	**Third-contact:** may be observed or recognised by patient/relative after consultation with the doctor or after receiving the Schedule V application form from the doctor
4	**Fourth-contact:** may be observed or recognised by POYC-MAS validating officer
5	**Fifth-contact:** may be observed or recognised only by POYC-MAS officer upon receiving the Schedule V application form
***Detectability:** the degree to which the potential failure mode may be observed or recognised using the above ordinal scale based on the Schedule V application procedure	

Appendix 7

RPNs for POYC-MAS Potential Failure Modes

Potential Failure Modes	Severity	Occurrence	Detectability	RPN
1.1 Prescriber did not apply for Schedule V	4	3	2	**24**
2.1 Prescriber used the wrong form	4	2	2	**16**
2.2 Prescriber did not apply for permit for protocol-regulated medicines	3	4	3	**36**
2.3 Prescriber did not sign application form	3	3	2	**18**
2.4 Prescriber's signature and other credentials not recognisable nor legible	4	3	2	**24**
2.5 Prescriber not eligible to apply for Schedule V or permit	4	3	3	**36**
2.6 Prescriber did not complete patient information for access and confirmation	4	3	2	**24**
2.7 Prescriber wrote the wrong patient information (for example, name and ID number not matching, C number for babies, F number for foreigners)	5	3	2	**30**

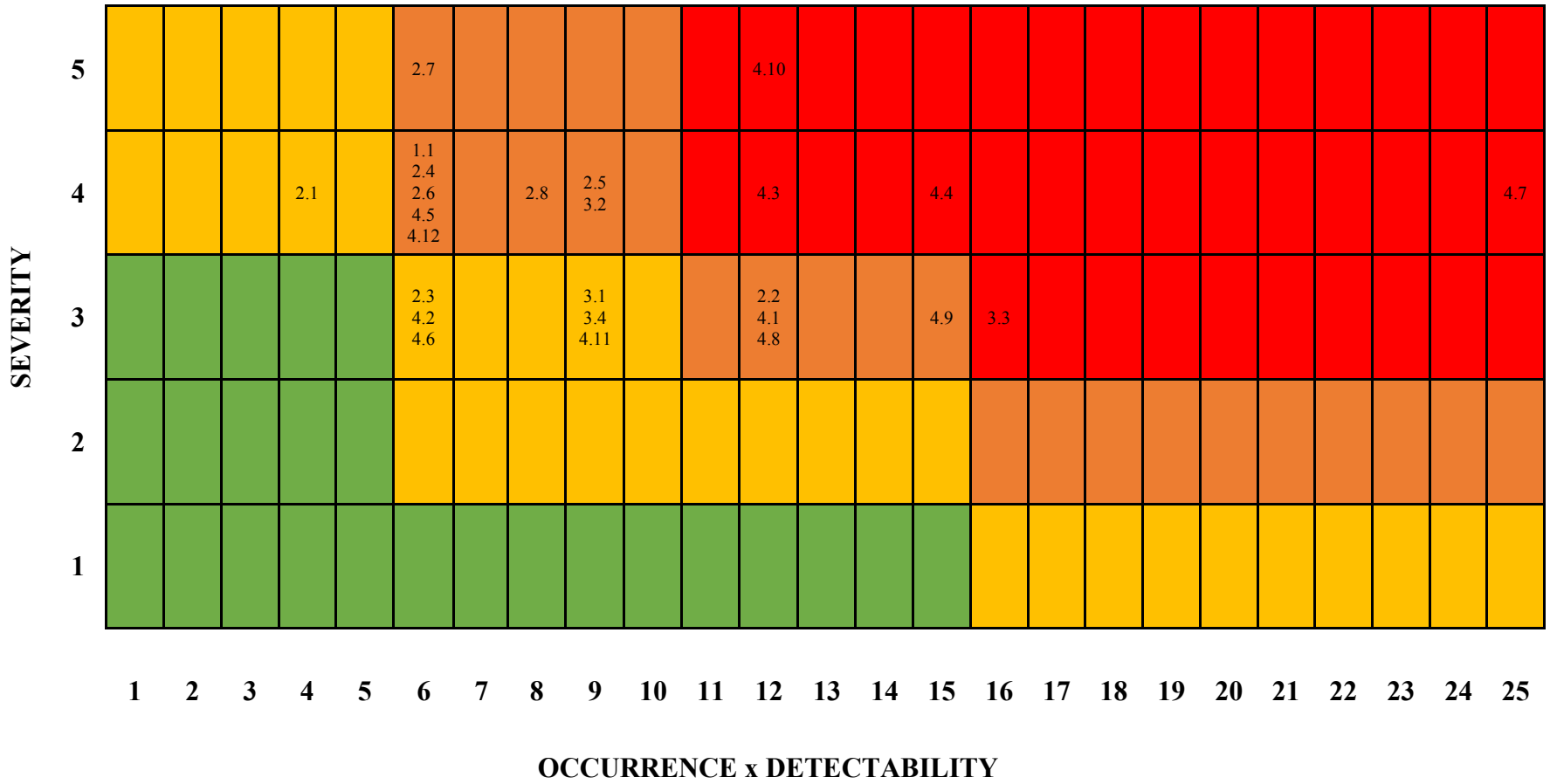
Potential Failure Modes	Severity	Occurrence	Detectability	RPN
2.8 Prescriber applied for non-protocol regulated medicines in Schedule V for patients who are not eligible in the scheme (for example, Asylum Seekers, Subsidiary Protection)	4	2	4	**32**
3.1 Patient failed to bring original application form (photocopies not accepted)	3	3	3	**27**
3.2 Patient submitted ticket of referrals or prescriptions instead of the application form	4	3	3	**36**
3.3 Foreign patient failed to bring supporting documents (for example, payslip, COE, pension slip) to confirm eligibility in the scheme	3	4	4	**48**
3.4 Patient did not present at POYC-MDH on the same day as the application	3	3	3	**27**
4.1 Medicine is not on the GFL	3	4	3	**36**

Potential Failure Modes	Severity	Occurrence	Detectability	RPN
4.2 Medicine is for in-patient use only	3	2	3	**18**
4.3 Wrong prescriber criteria	4	3	4	**48**
4.4 Medicine did not correspond to Schedule V condition	4	5	3	**60**
4.5 Prescriber applied for a condition that is not considered under Schedule V	4	2	3	**24**
4.6 Prescriber did not tick or indicate Schedule V condition or diagnosis in the application form	3	3	2	**18**
4.7 Application was not according to protocol	4	5	5	**100**
4.8 Application did not have the supporting document (for example, lipid profile, HbA1c test) as required by the protocol	3	4	3	**36**
4.9 Patients who benefit from Schedule II must renounce Schedule II before registering for Schedule V for diabetes mellitus medications	3	3	5	**45**

Potential Failure Modes	Severity	Occurrence	Detectability	RPN
4.10 Application was awaiting approval from the DPA for EMT	5	4	3	**60**
4.11 Medicine was not specified (for example, ACEI instead of specifying Enalapril, Perindopril)	3	3	3	**27**
4.12 Medicine listed not legible	4	3	2	**24**
Total Process RPN			**874**	

Appendix 8

Distribution of POYC-MAS Potential Failure Modes in a Risk Matrix


SEVERITY
5
4
3
2
1
2.7
4.10
1.1
2.4
2.6
4.5
4.12
2.1
2.8
2.5
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4.3
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4.2
4.6
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3.4
4.11
2.2
4.1
4.8
4.9
3.3
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18 19 20 21 22 23 24 25
OCCURRENCE x DETECTABILITY

Appendix 9

Mapping of Common Intervention Themes for POYC-MAS Potential Failure Modes

Potential Failure Modes	Interventions						
	Orientation Manual	Online Applications	Feedback System	Formulary and Protocol Review	Database Linking	Information Drive	Others
Critical Risks							
4.7 Application was not according to protocol			✓	✓			
4.10 Application was awaiting approval from the DPA for exceptional cases	✓		✓	✓		✓	
4.4 Medicine did not correspond to Schedule V condition		✓	✓				
4.3 Wrong prescriber criteria		✓	✓				
3.3 Foreign patient failed to bring supporting documents to confirm eligibility in the scheme	✓				✓	✓	
High Risks							
2.7 Prescriber wrote the wrong patient information (for example, name and ID number not matching, C number for babies)						✓	

Potential Failure Modes	Interventions						
	Orientation Manual	Online Applications	Feedback System	Formulary and Protocol Review	Database Linking	Information Drive	Others
2.5 Prescriber not eligible to apply for Schedule V or permit						✓	
3.2 Patient submitted ticket of referrals or prescriptions instead of the application form	✓					✓	
2.8 Prescriber applied for non-protocol regulated medicines in Schedule V for patients who are not eligible in the scheme (for example, Asylum Seekers, Subsidiary Protection)						✓	Availability of dedicated coordinator trained for such cases
1.1 Prescriber did not apply for Schedule V		✓				✓	
2.4 Prescriber's signature not recognisable nor legible		✓					
2.6 Prescriber did not complete patient information (for example, name, ID number, address, date of birth) for access						✓	Use of printed labels

Potential Failure Modes	Interventions						
	Orientation Manual	Online Applications	Feedback System	Formulary and Protocol Review	Database Linking	Information Drive	Others
4.5 Prescriber applied for a condition that is not considered under Schedule V		✓					
4.12 Medicine listed not legible		✓					
4.9 Patients who benefit from Schedule II (pink card) for diabetes treatment must renounce Schedule II before registering for Schedule V for diabetes mellitus medications	✓	✓				✓	
2.2 Prescriber did not apply for permit nor write protocol number for application of permit for protocol-regulated medicines		✓					
4.1 Medicine is not on the GFL		✓	✓	✓			
4.8 Application did not have the supporting document (for example, lipid profile, HbA1c test, case summary, control card) as required by the protocol					✓		

Potential Failure Modes	Interventions						
	Orientation Manual	Online Applications	Feedback System	Formulary and Protocol Review	Database Linking	Information Drive	Others
Moderate Risks							
2.1 Prescriber used the wrong form		✓	✓				
3.1 Patient failed to bring original application form (photocopies not accepted)		✓				✓	
3.4 Patient did not present at POYC-MDH on the same day as the application						✓	Increase in staff complement and office space
4.11 Medicine was not specified	✓	✓					
2.3 Prescriber did not sign application form		✓					
4.2 Medicine is for in-patient use only			✓				
4.6 Prescriber did not tick or indicate Schedule V condition or diagnosis in the application form		✓					